



Examination of the Regulation of *CXCL10* Expression, and *CXCL10* DNA Sequence Variation and Disease Associations

Hayriye Senturk Ciftci,¹ Meltem Savran Karadeniz¹, Fatma Savran Oguz¹,
Mehmet Tefvik Dorak²

¹ *Istanbul University, Istanbul Medical School, Istanbul Turkey;*

² *School of Health Sciences, Liverpool Hope University, Liverpool, U.K.*



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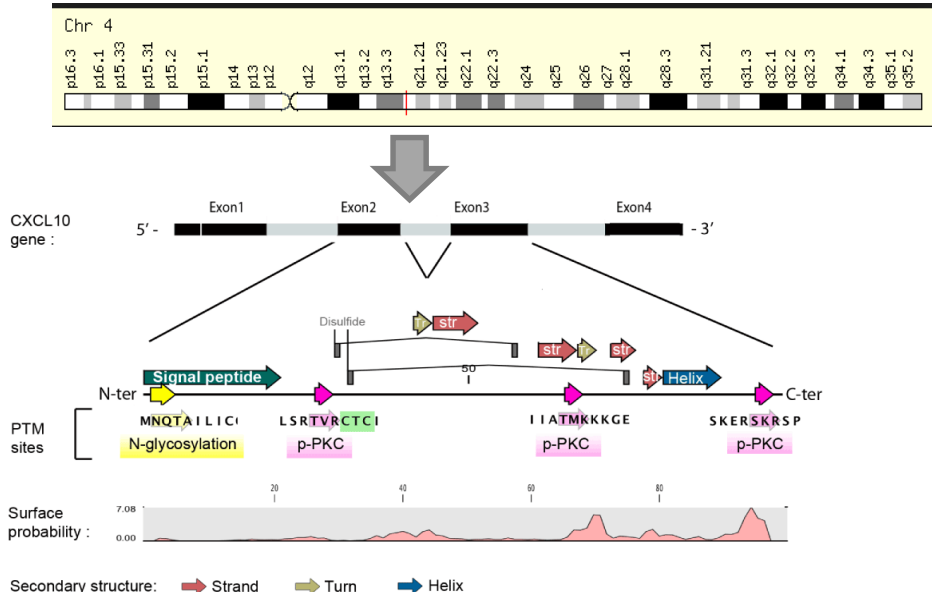
BACKGROUND

- **Chemokine proteins have important roles in inflammation and immunity.**
- **Chemokines are small, structurally related proteins which play a significant role in leukocyte trafficking by producing chemotactic activity in cells expressing corresponding chemokine receptors.**



BACKGROUND

- **CXCL10 (C-X-C Motif Chemokine Ligand 10)** is a member of the CXC chemokine family and binds to the CXCR3 receptor to exert its biological effects (chemotaxis, apoptosis, cell growth and angiostasis).
- ***CXCL10*** has been shown to be involved in the pathological processes of human disorders, infectious diseases, inflammatory and autoimmune diseases, and cancer.



AIM

**To learn about pathophysiological roles of CXCL10,
we aimed to examine:**

- **the regulation of expression of *CXCL10* (eQTL effects and miRNAs, co-regulated gene sets)**
- **disease associations of *CXCL10* sequence variants, eQTLs/meQTLs together with related miRNA variants**



METHODS

The CO-Regulation Database (CORD)
(co-expression analysis)

GSEA/MSigDB
(gene set enrichment analysis)

TargetScan
(miRNAs targeting *CXCL10*)

Blood eQTL Browser / BIOS / mQTLdb
(eQTLs and meQTLs targeting *CXCL10*)

GRASP
(disease associations of *CXCL10* and miRNA region SNPs)



RESULTS - CORD

CXCL10_co-expression analysis_CORD_5-fold.xlsx - Excel						
M.Tevfik DORAK						
File Home Insert Draw Page Layout Formulas Data Review View Foxit PDF Tell me what you want to do						
12						
	A	B	C	D	E	F
1	Gene symbol	Description	# of experiments with CXCL10	%concordant	Pearson Coeff	Pearson P value
2	CXCL10	chemokine (C-X-C motif) ligand 10 [Source:HGNC Symbol;Acc:10637]	645			
3	IFIT3	interferon-induced protein with tetratricopeptide repeats 3 [Source:HGNC Symbol;Acc:5411]	233	99.1416309013	0.707600045096	4.68879262475e-99
4	GBP1	guanylate binding protein 1, interferon-inducible [Source:HGNC Symbol;Acc:4182]	295	98.6440677966	0.676615860341	1.57213480546e-87
5	CXCL9	chemokine (C-X-C motif) ligand 9 [Source:HGNC Symbol;Acc:7098]	199	98.9949748744	0.623210684241	1.13031157134e-70
6	ISG15	ISG15 ubiquitin-like modifier [Source:HGNC Symbol;Acc:4053]	199	99.4974874372	0.616181242008	1.07892400193e-68
7	IFIT2	interferon-induced protein with tetratricopeptide repeats 2 [Source:HGNC Symbol;Acc:5409]	199	96.9849246231	0.612295127502	1.27692172513e-67
8	CXCL11	chemokine (C-X-C motif) ligand 11 [Source:HGNC Symbol;Acc:10638]	172	98.8372093023	0.610864771262	3.14353978454e-67
9	RSAD2	radical S-adenosyl methionine domain containing 2 [Source:HGNC Symbol;Acc:30908]	229	96.5065502183	0.591019041975	5.32102718365e-62
10	MX1	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse) [Source:HGNC	172	96.511627907	0.577574856907	1.16693763583e-58
11	IFIT1	interferon-induced protein with tetratricopeptide repeats 1 [Source:HGNC Symbol;Acc:5407]	233	91.8454935622	0.576605476943	2.00444042517e-58
12	ISG20	interferon stimulated exonuclease gene 20kDa [Source:HGNC Symbol;Acc:6130]	213	96.2441314554	0.564011071425	1.92490963693e-55
13	GBP2	guanylate binding protein 2, interferon-inducible [Source:HGNC Symbol;Acc:4183]	218	97.247706422	0.559873203422	1.72420509087e-54
14	STAT1	signal transducer and activator of transcription 1, 91kDa [Source:HGNC Symbol;Acc:11362]	194	96.3917525773	0.558116669552	4.3326732697e-54
15	MX2	myxovirus (influenza virus) resistance 2 (mouse) [Source:HGNC Symbol;Acc:7533]	182	96.7032967033	0.548643356317	5.67980848134e-52
16	IFI44	interferon-induced protein 44 [Source:HGNC Symbol;Acc:16938]	224	92.8571428571	0.543289612209	8.34519998925e-51
17	IFI44L	interferon-induced protein 44-like [Source:HGNC Symbol;Acc:17817]	178	93.8202247191	0.534117093494	7.46195399064e-49
18	OAS2	2'-5'-oligoadenylate synthetase 2, 69/71kDa [Source:HGNC Symbol;Acc:8087]	179	97.2067039106	0.52208839923	2.20195103352e-46
19	OAS1	2'-5'-oligoadenylate synthetase 1, 40/46kDa [Source:HGNC Symbol;Acc:8086]	173	95.9537572254	0.516159653331	3.34397228038e-45
20	IFIH1	interferon induced with helicase C domain 1 [Source:HGNC Symbol;Acc:18873]	166	100.0	0.50269136113	1.32828984062e-42
21	CCL5	chemokine (C-C motif) ligand 5 [Source:HGNC Symbol;Acc:10632]	181	99.4475138122	0.501353162858	2.37274562411e-42
22	CCL2	chemokine (C-C motif) ligand 2 [Source:HGNC Symbol;Acc:10618]	234	88.8888888889	0.487772436084	7.4155271901e-40
23	PLSCR1	phospholipid scramblase 1 [Source:HGNC Symbol;Acc:9092]	98	96.9387755102	0.474785908867	1.42361918658e-37
24	WARS	tryptophanyl-tRNA synthetase [Source:HGNC Symbol;Acc:12729]	88	96.5909090909	0.473458121373	2.40640717813e-37
25	LAMP3	lysosomal-associated membrane protein 3 [Source:HGNC Symbol;Acc:14582]	170	92.3529411765	0.4725245076	3.47591127372e-37
26	DDX58	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58 [Source:HGNC Symbol;Acc:19102]	147	99.3197278912	0.470593011346	7.41141992141e-37
27	SOD2	superoxide dismutase 2, mitochondrial [Source:HGNC Symbol;Acc:11180]	127	96.062992126	0.467790740409	2.20427090592e-36
28	RARRES3	retinoic acid receptor responder (tazarotene induced) 3 [Source:HGNC Symbol;Acc:9869]	124	95.1612903226	0.455142111183	2.6676593975e-34
29	IL6	interleukin 6 (interferon, beta 2) [Source:HGNC Symbol;Acc:6018]	242	79.3388429752	0.451632080556	9.74620777512e-34
30	APOL1	apolipoprotein L, 1 [Source:HGNC Symbol;Acc:618]	92	98.9130434783	0.448156546305	3.4641293989e-33
31	CXCL3	chemokine (C-X-C motif) ligand 3 [Source:HGNC Symbol;Acc:4604]	203	92.118226601	0.442066843445	3.08616961568e-32
32	TNFAIP2	tumor necrosis factor, alpha induced protein 2 [Source:HGNC Symbol;Acc:11806]	162	96.0225452274	0.421074181062	5.72086257121e-31
Experiments Concordant Discordant Concordant KEGG pathways Concordant COG Ontology ...						

The CO-Regulation Database (CORD): A Tool to Identify Coordinately Expressed Genes

John P. Fahrenbach, Jorge Andrade, Elizabeth M. McNally



RESULTS - CORD

- There were 182 concordantly co-expressed genes (at 5-fold threshold; $P < 5E-07$), including five additional CXCL genes (*CXCL2/3/9/11/13*) located in the same cytogenetic band as *CXCL10* (chr4q21)
- Ten MHC region genes were also strongly co-regulated, including *HLA-DRA/DQA1/DPA1* but not their beta-chain coding counterparts (*UBD, AIF1, IER3, C2, CFB, TAP2* and *HLA-DRB3* were the other MHC genes)
- The most highly significant co-expression pattern was noted in the spleen followed by other immune-related tissues and cells (neutrophils, thymus, B-cells)



The CO-Regulation Database (CORD): A Tool to Identify Coordinately Expressed Genes

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RESULTS - miRNA Targets

We selected the miRNAs targeting *CXCL10*, and determined their other target genes using TargetScan. Eighty miRNAs were identified, and the targets of each miRNA were identified to be used for GSEA analysis.

GSEA
Gene Set Enrichment Analysis

GSEA Home Downloads Molecular Signatures Database Documentation Contact

► MSigDB Home
► About Collections
► Browse Gene Sets
► Search Gene Sets
► **Investigate Gene Sets**
► View Gene Families
► Help

Investigate Gene Sets

Gain further insight into the biology behind a gene set by using the following tools:

- **compute overlaps** with other gene sets in MSigDB ([more...](#))
- **display the gene set expression profile** based on a selected compendium of expression data ([more...](#))
- **categorize** members of the gene set by gene families ([more...](#))

Gene Identifiers

RP11-1105G2.3
TFB2M
SAAL1
DCUN1D1
TBP
NDUFB2
ZNF117
IGFBP1
C1QBP
AC068987.1
CLEC1B
RD3L
TMEM185A
METTL21A
LIAS
GNG5
PPP1CC
GNG5P2
HEATR4
LINC00955
FOXC2
HAT1
EFEMP1
RP11-276H1.3
TDO2
SHC3
CTSS

Compute Overlaps

☐ H: hallmark gene sets [?](#)
☐ C1: positional gene sets [?](#)
☐ C2: curated gene sets [?](#)
☐ CGP: chemical and genetic perturbations [?](#)
☐ CP: Canonical pathways [?](#)
☐ CP: BIOCARTE: BioCarta gene sets [?](#)
☐ CP: KEGG: KEGG gene sets [?](#)
☐ CP: REACTOME: Reactome gene sets [?](#)
☐ C3: motif gene sets [?](#)
☐ MIR: microRNA targets [?](#)
☐ TFT: transcription factor targets [?](#)
☐ C4: computational gene sets [?](#)
☐ CGN: cancer gene neighborhoods [?](#)
☐ CM: cancer modules [?](#)
☐ C5: GO gene sets [?](#)
☐ BP: GO biological process [?](#)
☐ CC: GO cellular component [?](#)
☐ MF: GO molecular function [?](#)
☐ C6: oncogenic signatures [?](#)
☒ C7: immunologic signatures [?](#)

show **top 10** genesets

with FDR q-value below

[compute overlaps](#)

Compendia expression profiles

☒ Human tissue compendium (Novartis)
☐ NCI-60 cell lines (National Cancer Institute)

[display expression profile](#)

Gene families

[show gene families](#)



RESULTS - GSEA

The gene set enrichment analysis of the co-expressed gene set suggested enrichment of genes involved in breast and prostate cancers, immune and inflammatory response, and response to interferon and regulatory T cells ($\text{FDR} < 10^{-50}$)

The co-expressed gene set did not have enrichment for cumulative targets of any miRNA that target *CXCL10*



RESULTS - GWAS

Examination of disease associations of SNPs from each miRNA gene region in GWAS databases yielded results for autoimmune (RA, AS, CD, psoriasis, MS, T1D, MG, GD) disorders and allergy/asthma ($P < 10^{-4}$)

SNPs within *CXCL10* did not show any GWAS associations

SNPs acting as eQTL/meQTL in blood for *CXCL10* showed GWAS associations with longevity, aging, IBD and breast cancer ($P < 10^{-4}$)



CONCLUSIONS

We did not find strong evidence for miRNA-mediated *CXCL10* expression, but the variants near miRNAs showed stronger genetic associations with inflammatory and immune disorders.

We conclude that the role played by *CXCL10* is stronger in autoimmunity, inflammation and possibly cancer than in transplantation.

This study shows the feasibility of preliminary dry laboratory projects before launching wet laboratory experiments.





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