RESEARCH

In silico discovery of blood cell macromolecular associations

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Abstract

Background: Physical molecular interactions are the basis of intracellular signalling and gene regulatory networks, and comprehensive, accessible databases are needed for their discovery. Highly correlated transcripts may reflect important functional associations, but identification of such associations from primary data are cumbersome. We have constructed and adapted a user-friendly web application to discover and identify putative macromolecular associations in human peripheral blood based on significant correlations at the transcriptional level.

Methods: The blood transcriptome was characterized by quantification of 17,328 RNA species, including 341 mature microRNAs in 105 clinically well-characterized postmenopausal women. Intercorrelation of detected transcripts signal levels generated a matrix with > 150 million correlations recognizing the human blood RNA interactome. The correlations with calculated adjusted *p*-values were made easily accessible by a novel web application.

Results: We found that significant transcript correlations within the giant matrix reflect experimentally documented interactions involving select ubiquitous blood relevant transcription factors (CREB1, GATA1, and the glucocorticoid receptor (GR, NR3C1)). Their responsive genes recapitulated up to 91% of these as significant correlations, and were replicated in an independent cohort of 1204 individual blood samples from the Framingham Heart Study. Furthermore, experimentally documented mRNAs/miRNA associations were also reproduced in the matrix, and their predicted functional co-expression described. The blood transcript web application is available at http://app.uio.no/med/klinmed/correlation-browser/blood/index.php and works on all commonly used internet browsers.

Conclusions: Using in silico analyses and a novel web application, we found that correlated blood transcripts across 105 postmenopausal women reflected experimentally proven molecular associations. Furthermore, the associations were reproduced in a much larger and more heterogeneous cohort and should therefore be generally representative. The web application lends itself to be a useful hypothesis generating tool for identification of regulatory mechanisms in complex biological data sets.

Keywords: Blood, Transcriptome, Web application, Molecular associations, Microarrays

Background

Regulation of human gene expression relies on functional macromolecules, including transcription factors (TFs), and micro RNAs (miRNAs). TFs may induce or suppress transcription of their target genes, exerted via distinct binding sites and interaction with other signalling molecules [1]. miRNA's main function is inactivation of mRNAs [2]. Our hypothesis is that highly correlated

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transcripts in blood and tissue may reflect important functional associations and be a useful tool for hypotheses generation. Signal molecules are often involved in the same pathways and likely to be similarly regulated [3, 4]. We have used the global transcriptome generated from peripheral blood donated by an Oslo cohort of 105 postmenopausal women who were similar with respect to age, ethnicity and health status to generate a large correlation matrix with Pearson r values and modes of significance based on transcription signal values. A web application was developed to explore associations between genes of interest in the dataset.

Coexpressed transcripts tend to reflect co-expressed proteins [5] and we hypothesized that highly correlated transcripts could reflect associations at the protein level. Three ubiquitously expressed TFs known to be functionally important in blood cells were used for testing: cyclic AMP-responsive element (CRE)-binding protein 1 (CREB1), GATA Binding Protein 1 (GATA1) and glucocorticoid receptor (GR). CREB1 is involved in several aspects of hematopoiesis [6–9]. DNA binding and activation of CREB1 depends on its phosphorylation, for example induced by parathyroid hormone (PTH) [10]. Furthermore, expression of *CREB1* in peripheral blood mononuclear cells (PBMC) correlates positively with *CREB1* expression in the postmortem brain of Alzheimer's patients [11]. Thus, identification of associated transcripts may help to identify novel TFs and their gene targets of functional importance in blood and other tissues. In fact, three datasets of gene expression in immortalized B cells from normal individuals were used to show that correlated transcript levels could be used to predict gene function [12]. GATA1 is essential for erythroid development by regulating the switch of fetal hemoglobin to adult hemoglobin in haemopoietic cells. *GATA1* is a multifunctional gene regulating a plethora of genes, and Encyclopedia of DNA Elements (ENCODE) has registered its response element in nearly 10,000 genes.

The glucocorticoid receptor (GR, *NR3C1*) is also expressed in most tissues and cells, modulating activities of genes involved in cell differentiation/development, metabolism, and immune responses [13]. Natural forms of glucocorticoids or analogs like dexamethasone, all acting through GR, are frequently used medical drugs with direct effects on almost all cell types [14]. Even in physiological concentrations, glucocorticoids regulate major aspects of immune cell functions and are powerful immunosuppressants at pharmacological doses [15].

We also verified the representativeness of our dataset by replicating the top 200 associations in an independent cohort from the Framingham study. Furthermore, we tested if experimentally proven miRNA/mRNA associations, also were statistically correlated in our dataset.

Construction and content
Blood donors
For the postmenopausal blood sampling, Norwegian women (50–86 years, $n = 105$) representing a cohort with varying bone mineral densities (BMDs) and free of primary diseases known to affect the skeleton, were consecutively recruited as described [16]. Blood was collected in the morning from fasting individuals. Postmenopausal women from the Offspring cohort (women aged 40–92, $n = 1204$) participating in The Framingham Study [17, 18] were used as replication cohort. The Framingham Heart Study (FHS) is an ongoing prospective community-based study that includes the children of the original cohort and their spouses, who were enrolled into the Offspring Cohort in 1971. At each FHS examination, age, height, weight and extensive questionnaires were obtained according to standardized protocols. For this analysis, we included Offspring participants who attended examination cycle 8 (2005–2008). Gene expression data was collected for ($n = 2442$) as previously described [18, 19]. These were further filtered on female sex and menopause to achieve the final sample size ($n = 1204$). Of note, hormone replacement therapy was not included in filtration criteria.

RNA purification and gene expression analysis
RNA from whole blood was isolated according to the PAXgene Blood RNA Kit manufacturer (BD, Franklin Lakes, NJ, USA), including the optional on-column DNase digestion according to manufacturer's instructions. RNA from the Oslo and Framingham cohorts were analysed according to manufacturer's instructions on the Affymetrix Human Gene 1.0 ST GeneChip (Thermo Fisher Scientific, Waltham, MA, USA) which contains ~1.4 million probe sets in total. In brief, the Affymetrix Human Exon 1.0 ST Array (Affymetrix, Inc., Santa Clara, CA) was used and gene annotations were obtained from Affymetrix NetAffx Analysis Center (version 31), resulting in ~17,000 distinct genes for downstream analysis.

A PCR based method involving LDA cards A and B was used for quantification of ~700 microRNAs and other non-coding RNAs in the Oslo cohort according to manufacturer's instructions (Thermo Fisher Scientific, Waltham, MA, USA).

Calculations, statistics and the web application
Pearson product-moment correlation coefficients (r) were computed between expressions of all genes (>17,000 probe sets) across 105 women using $\log_2$ transformed Affymetrix RMA (Robust Multi-array Average) signal values and inversed PCR Ct values and saved in a database along with their corresponding *p*-values. A

web application publicly available at http://app.uio.no/med/klinmed/correlation-browser/blood/index.php was programmed in order to access the database and flexibly search for correlations of interest as previously described [20]. A screenshot of the web application is displayed in Fig. 1. Search results are returned together with raw and Bonferroni-corrected *p*-values and a measure of the false discovery rate (FDR) as estimated by the Benjamini & Hochberg procedure [21]. This procedure has been shown to control FDR when the tests are independent or positively correlated [22]. This assumption is reasonable when identifying differentially expressed genes. The Oslo cohort generated expression data earlier and was the basis for development of the web application. When other expression data became available later, the Framingham data was selected for replication because of similarity with regard to the platform. In the replication analysis, we computed Pearson product moment correlations, followed by Bonferroni correction. Algorithm and methods used in generation of the web application have been more thoroughly described in a previous similar paper [20].

Utility
Verifications
First, we identified the 200 most significantly correlated transcripts for each of the selected transcription factors (CREB1, GATA1, GR) and second, tested if associations identified by the web application reflected experimentally verified interactions. Then, we analysed if the genes harboured the corresponding transcription factor binding sites in their promoters. For this we used ENCODE summarizing results from Chromatin Immunoprecipitation (ChIP) studies by use of the Harmonizome web portal (https://maayanlab.cloud/Harmonizome/gene_set/NR3C1/ENCODE+Transcription+Factor+Targets) [23].

Promoter elements binding CREB1 protein, were identified in 182 of the 200 (91%) topmost CREB1 correlated genes (Table S1), In contrast, when selecting random genes from the same Oslo cohort, 48.3% (SD = 2.1%) were identified as having a CREB1 promoter element (not shown). In all, 13,251 genes have this element as registered by ENCODE, thus, a high fraction of associations are expected for sets of random genes. Similar results were obtained for GATA1 with binding elements found in 73.0% while 34.5% (SD = 6.1) binding elements were found in 200 random genes (Table S2). For GR 35.5% of 200 topmost correlated genes had the GR binding element while random genes had 14.0% (SD = 3.0) binding sites (Table S3). ENCODE have registered 9608 and 4104 genes with binding sites for GATA1 and GR, respectively.

We tested representativeness of the Oslo cohort by checking if the 200 most significant associations in the Oslo cohort were reproduced in blood from post-menopausal women at exam 8 in Framingham Study (*N* = 1204). For CREB1, 180 associations reached significance also in the Framingham cohort (six did not reach significance, and 14 transcripts were undetected) (Table S1). For GATA1 and GR, all, but five and four of the transcripts detected in both cohorts reached statistical significance in the Framingham cohort (Tables S2 and S3, respectively).

Evaluation of associations involving microRNAs
To verify whether the web application/matrix can identify also putative miRNA targets, we took advantage of experimentally proven miRNA targets in TarBase 8.0 using DIANA Tools (https://carolina.imis.athena-innovation.gr/diana_tools/web/index.php?r=tarbasev8%2Findex) [24]. For each of the ten miRNAs most highly expressed in peripheral blood based on their PCR Ct-values, the 20 best experimentally verified interacting mRNAs, accessing all cell lines and tissues, were obtained. Out of the ~200 interactions/associations, 50 (25%) appeared as nominally significant when analysed in the web application (Table S4). As an alternative evaluation strategy, we selected the top 50 experimentally verified miRNA/mRNA interactions in blood from TarBase 8.0, and found that 30 pairs reached detection level in the Oslo cohort and 13 (43%) of these obtained nominal significance (Table S5).

Analysis of the blood interactome employing ingenuity pathway analysis (IPA)
Initially, we tested whether experimentally proven, functional associations mapped by IPA were reproduced in our data. As presented in Table S6, transcripts associating with CREB1 as well as GATA1 were statistically over-represented in functions related to haematological systems within the category "Physiological System Development and Function" As expected, more

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(See figure on next page.)
Fig. 1 Interface of the web application. A typical search starts with inserting an identifier in the first window of "Search Options", either Entrez Gene ID (e.g., "1234"), an Accession Number (e.g., "BE644809" or "NM_005715"), a Gene Symbol (e.g., "NR3C1" or "CREB1", not case-sensitive) or an Affymetrix probe set ID (e.g., "8,114,814"). Then, a specific transcript can be traced by inserting a second identifier in window two under "Search Options". Alternatively, the window may be left open to obtain a list of the transcripts most significantly correlating to the identifier in the first window. Filling in boxes in the "Output Options" fields enables restriction of output to e.g., transcripts having specific keywords in Gene Ontology (GO), TFs (genes having "transcription" as part of the Gene Title) or only positive or negative correlations

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[Correlation Browser / New Search] [List of best correlations] [List of all variables]

Correlations in the blood dataset

A typical search starts with inserting an identifier in the first window of "Search Options", either Entrez Gene ID (e.g., "1234"), an Accession Number (e.g., "BE644809" or "NM_005715"), a Gene Symbol (e.g., "NR3C1" or "CREB1", not case-sensitive) or an Affymetrix probe set ID (e.g., "8114814").

Then, a specific transcript can be traced by inserting a second identifier in window two under "Search Options". Alternatively, the window may be left open to obtain a list of the transcripts most significantly correlating to the identifier in the first window.

Filling in boxes in the "output options" fields enables restriction of output to e.g., transcripts having specific keywords in Gene Ontology (GO), TFs (genes having "transcription" as part of the Gene Title) or only positive or negative correlations.

(View the full list of available key terms [here]).

Search Options: Find correlations between...		
Gene/Label/Number: NR3C1	and all others	(Empty also means "all others")
Output Options		

Restrict output to ☐ miRs, ☐ Transcription factors? (Empty: No restrictions.)

GO: all Ontologies ⌄ with keyword: anything

KEGG Pathway: any

Limit output to 50 rows.

Remove ☑ "self correlations", i.e. correlations of a variable with itself

Sort results by ○ positive, ○ negative or ⦿ absolute value of correlation

Clear form | Find correlations

Starting timer.
Connected to database on
Searching for user input in variable labels, Entrez IDs, Accession Numbers...
Evaluating targets, filters and restrictions...

Finding correlations with 1 variable:					
id	Label1	AccNum	GeneSym	Info	Gene Name
14821	8114814	NM_000176	NR3C1	ⓘ	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)

Fetching correlation data, please wait...
Getting list of correlations for id 14821.
Getting list of p-values for id 14821.
1 of 1 done.
Calculating corrections for multiple testing (n=17327), please wait...
Done; whole program took 0.793 seconds. Transmitting 50 results:

Column legend:

- Rank: Row number sorted by strongest correlation
- Label1: Affymetrix probe set identifier(s) of the gene used in the search
- Label2: Affymetrix probe set identifiers of genes correlating to the Label 1 gene
- AccNum: The unique identifier for a sequence record [accessible at NCBI]
- GeneSym: Official gene symbol
- Info: Link to more information about the variable in the given row
- Pearson r: Pearson correlation coefficient
- Raw p: Unadjusted p-value
- Bonferroni: Bonferroni corrected p-value
- FDR (BH): False Discovery rate calculated by the Benjamini-Hochberg Procedure

Rank	Label1	Label2	AccNum	GeneSym	Info	Pearson r	Raw p	Bonferroni	FDR (BH)
1	8114814	8105681	NM_018695	ERBB2IP	ⓘ	0.924976	4.449643e-45	7.709896e-41	7.709896e-41
2	8114814	7967420	NM_018183	SBNO1	ⓘ	0.922925	1.693471e-44	2.934277e-40	1.467138e-40
3	8114814	8084016	NM_006218	PIK3CA	ⓘ	0.922862	1.762664e-44	3.054167e-40	1.018056e-40
4	8114814	8045919	NM_022826	MARCH7	ⓘ	0.921074	5.479506e-44	9.494339e-40	2.373585e-40
5	8114814	8050565	NM_015317	PUM2	ⓘ	0.920808	6.470525e-44	1.121148e-39	2.242296e-40
6	8114814	8059393	NM_003590	CUL3	ⓘ	0.916449	9.136088e-43	1.583010e-38	2.638350e-39
7	8114814	7972062	NM_012158	FBXL3	ⓘ	0.916036	1.165136e-42	2.018830e-38	2.884043e-39
8	8114814	7933947	NM_022079	HERC4	ⓘ	0.914671	2.580860e-42	4.471856e-38	5.589820e-39
9	8114814	8169541	NM_144658	DOCK11	ⓘ	0.914475	2.890279e-42	5.007986e-38	5.564429e-39
10	8114814	8115022	NM_001025105	CSNK1A1	ⓘ	0.911164	1.876191e-41	3.250877e-37	3.250877e-38
11	8114814	7968274	NM_175854	PAN3	ⓘ	0.911027	2.023974e-41	3.506940e-37	3.188127e-38
12	8114814	8091048	NR_023350	COPB2	ⓘ	0.910830	2.256134e-41	3.909203e-37	3.257669e-38
13	8114814	7932911	NM_004521	KIF5B	ⓘ	0.909288	5.243304e-41	9.085073e-37	6.988517e-38
14	8114814	8052443	NM_014709	USP34	ⓘ	0.908977	6.202173e-41	1.074650e-36	7.676075e-38

Fig. 1 (See legend on previous page.)

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general functions were attributed to the genes most strongly associated with GR. Furthermore, in the inter-correlation network generated by IPA, all the tested transcriptional regulators (CREB1, GATA1, and GR) had a very central position in the respective top ranked networks (Figs. S1, S2 and S3), supporting that the detected associations were real.

Discussion

We hypothesized that highly correlated blood cells transcripts could be functionally associated in our dataset and that these associations could be easily assessed by a user-friendly web application. We explored significant macromolecular associations involving CREB1, GATA1 and GR transcription factors. The in silico associations were supported using ENCODE ChIP data from both tissues and cells unrelated to blood, indicating a common functionality irrespective of cell or tissue type. The finding that fewer significant GR correlations (71/200, Table S3) were identified in ENCODE compared to CREB1 (182/200, Table S1) and GATA1 (146/200, Table S2) may be related to GR being able to bind other transcription factors, e.g., those binding to The Activator Protein-1 (AP-1) sites (Fos, Jun and others) without binding directly to DNA [25]. For example, only 62% of dexamethasone induced GR binding sites contained the GR response element when dexamethasone induced transcription was studied in A549 cells [26]. Since thousands of human genes harbour DNA binding elements for the tested transcription factors, we expected to find such elements also in several randomly tested genes used as control, but significantly less. The very high overlap in transcript association between the Framingham and Oslo cohorts, confirmed the validity of the results obtained using in silico analyses. Correlation estimates from the Oslo cohort were generally somewhat higher than in the Framingham dataset, and the difference may be related to a more heterogenous Framingham cohort with respect to age, ethnicity and health status. As expected, experimentally verified mRNA/miRNA associations were not reproduced equally well as mRNA/mRNA associations in our data. This is probably because cell/tissue specific sets of miRNAs are needed to target and degrade mRNAs [2]. Sets of miRNAs targeting specific mRNAs identified in other cohorts and/or tissues may not be present in peripheral blood. Thus, we consider replication of 25% (Table S4) and 43% (Table S5) of verified miRNA/mRNA interactions as satisfactory. The results underscore the usefulness of the in silico approach and web application for detection of miRNA/mRNA associations in peripheral blood, but appear also to have relevance for other tissues. We assume that

associations identified are relevant for both sexes, but this needs to be verified.

Conclusion

The results indicate that in silico analyses using a large correlation matrix containing the blood transcriptome associations in combination with a user-friendly web application, may identify functionally associated macromolecules in blood with relevance also for tissues.

Supplementary Information

Availability of data and materials
The normalized PCR and Affymetrix signal values used for generation of data accessible in the web application are available in Table S7. The application is available at: http://app.uio.no/med/klinmed/correlation-browser/blood/index.php The primary data used in the web application have also been deposited in NCBI's Gene Expression Omnibus [27], accessible through GEO Series accession number GSE198941 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE198941).

Declarations

Ethics approval and consent to participate
Prior to the study, approval was obtained by the Norwegian Regional Ethics Committee (REK 2010/2539) for the Oslo cohort and by Boston University Medical Center Institutional Review Board for the Framingham cohort. The study was conducted according to the Declaration of Helsinki (2000). Sampling and procedures followed the National laws after obtaining verbal and written, informed consent. The verbal informed consent obtained from the participants were approved by the Norwegian Regional Ethics Committee (REK 2010/2539) and Boston University Medical Center Institutional Review Board. Validation data was made available from dbGaP through approved request number 1302685–1.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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