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Interleukins as a Common Indicator for the Effects of Both Weather and Obesity on Human Health

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Abstract

The influence of weather on human health has been studied for diseases including stroke and ischemic heart disease. The effect of obesity on human health has also been reported, and a connection to insulin resistance has been discussed as a main cause of ischemic diseases. Thus meteorological factors and obesity threaten human health leading to disease such as stroke and ischemic heart diseases.

However, there has been no common measure to evaluate the effects both of meteorological factors and obesity simultaneously. In this paper, we propose, as a candidate for this measure, the evaluation of gene expression of interleukins including interleukin 6 (IL-6). Interleukins are a group of small proteins and a subgroup of cytokines, which are important for communications among cells. We extracted from the Gene Expression Omnibus (GEO) database several datasets of experiments associated with cold exposure and fat diet. As a method to measure the variability of gene expressions, we used the method of log2-Fold Change (log2FC), which was known as a basic method of normalization and transformation for microarray data. To investigate a common measure of the effects of cold exposure and obesity, we examined the gene expression of interleukins and found the increase of interleukin-related genes played an important role in inflammatory reactions.

We conclude that interleukins, including IL-6, can be a candidate for common indicators of both weather effects and obesity on human health. Our findings, together with a recent supply of simple kits to measure interleukins, may contribute to making a system to avoid the onset of diseases including stroke and ischemic heart diseases.

Keywords: Cytokine; Interleukin; Gene expression; Cerebral infarction; Ischemic heart disease

Introduction

Many studies have suggested the influences of weather on the incidence of stroke and ischemic heart disease [1]. Daily meteorological factors have been used to investigate the links between weather and these diseases by linear regression methods. The onset of these diseases has been suggested to be related to temperature, atmospheric pressure and humidity [2]. Recently, methods of data mining were applied to this issue. For example, a hidden Markov model was implemented and hidden states of weather associated with the onset of diseases were identified [3,4].

In fat tissues of obese individuals, more tumor necrosis factor alpha (TNF-alpha) mRNA was observed compared with lean controls [5,6]. As a result, insulin resistance is induced [6]. The increase in TNF-alpha also induces gene expression of interleukins such as IL-6 [7]. IL-6 stimulation then induces ICAM-1 and vascular endothelial growth factor (VEGF) expressions and leads to human duodenal fibroblasts [7]. Thus human obesity has a connection to insulin resistance and ischemic diseases.

Meteorological factors and obesity both affect human health leading to stroke or ischemic heart diseases. However, there have been no common measures to evaluate the effects of meteorological factors and obesity at the same time. In this paper, we propose as a candidate for this measure, the evaluation of gene expression of interleukins including IL-6 [8,9].

Abundant gene expression data based on experiments using microarrays are now stored in a public functional genomics data repository, the Gene Expression Omnibus (GEO) maintained by the National Center for Biotechnology Information (NCBI). We extracted from this database several results of experiments associated with cold exposure and fat diet respectively. As a method to measure the variety of gene expression, we used the calculation of log2-Fold Change (log2FC), which was known as a basic method of normalization and transformation for microarray data.

We concentrated our attention on the genes of interleukins, a subgroup of cytokines. Cytokines are small secreted proteins released by cells and have a specific effect on the interactions and communications between cells. Proinflammatory cytokines are produced predominantly by activated macrophages and are involved in the up-regulation of inflammatory reactions. Interleukins are cytokines which are made by one leukocyte and act on other leukocytes. The function of the immune system depends in a large part on interleukins. There are both proinflammatory interleukins (e.g., IL-1, IL-6) and anti-inflammatory cytokines (e.g., IL-10).

The effect of weather on interleukins was reported [9,10] and the influence of obesity was identified by several reports [5-7]. The cytokine network was suggested as a bridge for the effects of weather and obesity [11]. If a significant change in gene expression of

interleukins can be found among log2-fold changes as a result of weather and obesity, then it will deliver a common table to measure the effects of both weather and obesity simultaneously. Thus, the observation of interleukins will contribute to preventing the onset of diseases including stroke and ischemic heart disease.

Method

A microarray is a laboratory instrument used to detect the expression of extreme numbers of genes at the same time. DNA microarrays are microscope slides that are printed with tiny spots in defined positions, with each spot containing a known DNA sequence or gene. The DNA molecules attached to each slide perform as probes to show gene expression, especially RNA (mRNA) transcripts expressed by a group of genes.

To perform a microarray analysis, mRNA molecules are collected from both an experimental sample and a reference (or control) sample. For example, the reference sample could be collected from a healthy individual, and the experimental sample could be collected from an individual with a disease. The two mRNA samples are then converted into complementary DNA (cDNA), and each sample is labeled with a fluorescent probe of a different color. The microarray is scanned to measure the expression of each gene printed on the slide. The data collected through microarrays can be used to supply gene expression profiles, which show simultaneous changes in the expression of many genes in response to a particular condition or treatment. The microarray data of gene expression have been stored in the GEO maintained by the NCBI. The NCBI is a database (called GenBank) of DNA sequences providing access to biomedical and genomic information. GEO is a public functional genomics data repository organized by NCBI and stores curated gene expression datasets obtained from microarrays.

Identification of variance of gene expressions was performed by a method, "log2-fold change" (log2FC or logFC). If there are two numbers X and Y, the fold change (FC) is defined as a fraction X/Y. Taking log2 (log with base 2) of this ratio, the log2-FC is expressed as log2(X/Y). The log2FC is often used in analysis of gene expression data in microarray and RNA-Sequence experiments, for measuring change in the expression level of a gene [12].

In the field of genomics (and more generally in bioinformatics), X and Y represent a group or vector of different categories of samples. A microarray dataset consists of a matrix, with rows representing genes and columns representing samples. For example, a typical microarray dataset forms a matrix of 50 thousand rows and 10 columns representing samples of two experimental conditions, A and B (e.g., 5 columns are cases and 5 columns controls). The results of log2-FC represent changes of gene expressions between two experimental conditions, A and B. Selecting all possible combinations (a so-called "round-robin") of pairs (x, y) of samples taken from each group with x from A and y from B, one calculates the geometrical means of $\log_2$(xki/ykj) where xki and ykj represent i-th or j-th member of each group among k-th row. In real calculations, the process includes the calculation of rank for each column of microarray matrix data. Therefore, the results depend on rows, i.e., the calculation cannot be done for each row independently.

We used the software R and its packages, "RMA", "Limma" and "DESeq2" for normalization of gene expression data and for the calculation of log2-FC. Each package was selected according to the format of gene expression data.

Results

We extracted six gene expression datasets from the GEO. The accession numbers were GSE13432, GSE40486, GSE70437, GSE15773, GSE65557, GSE71367. The former three datasets were used to investigate the effects of cold exposure. The latter three datasets were used to examine the effects of fat diet.

The data of accession number GSE13432 were originally supplied to the GEO by Xue [13]. The original experiment was intended to investigate molecular mechanisms of angiogenesis in relation to adipose tissue metabolism. They exposed adult mice (C57/Bl6) to 4°C for up to 5 weeks and extracted white adipose tissue. Control mice were maintained at the thermoneutral temperature of 30°C. We used these data, especially raw data, to examine the effects of cold exposure to the network of interleukins. Therefore, in this study, the control is mice exposed to 30°C for one week, and the case is mice exposed to 4°C for one week.

The raw data were analyzed by methods supplied by "Bioconductor", a collection of useful packages for analysis of gene data written in the software R. After extracting raw data from GEO, the data were normalized by "rma". First, the calculation of log2-FCs was performed for all genes using R-package "lemma". Then the results for interleukins were selected.

The results of log2-FCs for interleukins are shown in Table 1, where the values of "log2fc" express the variations between the case of cold exposure and the control (Table 1).

ID	Symbol	$\log_2$fc	pvalues
1421239_at	Il6st	0.938685403	0.003139557
1450273_at	Il1rl2	0.624190565	4.55E-05
1419671_a_at	Il17rc	0.585488043	0.006793532
1452109_at	Il17re	0.462319019	8.25E-05
1423996_a_at	Il4ra	0.439752649	0.005843369
1422397_a_at	Il15ra	0.371886615	0.007432892
1417948_s_at	Ilf2	-1.216359024	2.82E-05
1416200_at	Il33	-1.309043304	7.71E-05
1434903_s_at	Il1rl2	-1.449838852	0.000238614
1454783_at	Il13ra1	-1.578592165	0.000246853
1448575_at	Il7r	-1.696383537	0.000584202
1448576_at	Il7r	-1.730123188	0.000758495

Note: "ID" means ID of genes in the microarray, "Symbol" means the symbols of genes (related to interleukins), "log2fc" means the log2-FC, and "pvalues" means p-values that show the stochastic significance of the value of "log2fc"

Table 1: The log2-FCs of interleukin-related genes in GSE13432.

In Table 1, we see that the log2-FC of the gene expression of the interleukin 6 signal transducer (Il6st) is almost 1. This means that the gene expression of cold-exposed mice increased twofold. The genes related to interleukin 1 (Il1) and interleukin 17 (Il17) also increased. Interleukin 6 (IL-6) is known to activate macrophage, and interleukin 17 (IL-17) IL-17 activates several positive cascades and leads to the

induction of severe rheumatism [14]. Since the negative value of log2-FC implies "decrease" of gene expression, we observe that the genes related to interleukin 7 and 13 decreased in expression. The interleukin 7 is known to cure lymphopenia.

The data of accession number GSE40486 was provided to the GEO by Plaiser [15]. C57BL/6J mice were exposed to 4°C for 4 hours. The microarray data were extracted from brown adipose tissues (BAT) and skeletal muscle. Data of control mice were supplied with the name "RT" in the same accession number. They found that the Zbtb16 mRNA levels increased in both BAT and skeletal muscle after cold exposure. Here, we used "RT" as control and BAT from mice exposed to 4°C for 4 hours as case.

The normalization and calculation of log2-FCs were performed by "DESeq2" [16]. The results are shown in (Table 2).

ID	Symbol	log_2fc	pvalues
ILMN_2610234	Il15	1.646604899	1.78E-14
ILMN_2770260	Il17rb	0.664276602	0.057498872
ILMN_2608184	Il6st	0.333244725	0.041454415
ILMN_2707401	Ilf3	-0.59410005	0.084376557
ILMN_1233822	Ilf3	-0.712344207	0.005487237
Note: The format of data in this table is the same as that of Table 1 "Ilf3" is interleukin enhancer binding factor 3			

Table 2: The log2-FCs of interleukin-related genes in GSE40486.

The up-regulated genes are Il15, Il17rb and Il6st, and the down-regulated gene is Ilf3. The gene Il15 represents interleukin 15 (IL-15) and is a cytokine that regulates T and natural killer cell activation and proliferation. This cytokine and interleukin 2 share many biological activities. Il17rb is the gene interleukin-17 (IL-17) receptor B. Il6st is interleukin 6 (IL-6) signal transducer. Ilf3 is interleukin enhancer binding Factor 3 and encodes an RNA binding protein that complexes with other proteins to regulate gene expression and stabilize mRNAs.

The data of accession number GSE70437 was uploaded to the GEO by Marcher [17]. The data contained gene expression data of mice kept at either 4°C or 22°C for three days. The microarray data were extracted from interscapular brown adipose tissue (iBAT). We used the method "DESeq2", and the results are shown in (Table 3).

ID	Symbol	log_2fc	pvalue
NM_013563	Il2rg	1.1530705	5.59E-07
NM_008359	Il17ra	0.96358305	7.78E-06
NM_031167	Il1rn	0.923245002	0.007836533
NM_016671	Il27ra	0.84829895	0.015196062
NM_001159318	Il1rap	0.730641672	0.041860418
NM_001254747	Il15	0.715014468	0.00061216
NM_031252	Il23a	0.687624725	0.043504201
NM_010554	Il1a	0.684464516	0.043008585
NM_178942	Il17rc	0.677900267	0.001318711
NM_008362	Il1r1	0.57127273	0.001429907
NM_001008700	Il4ra	0.544350192	0.000145806
NM_010561	Ilf3	-0.376843137	0.000960897
NM_010551	Il16	-0.58180201	0.029881387
NM_019583	Il17rb	-0.581807875	0.076177452
NM_001025602	Il1rl1	-0.590478935	0.078347154
NM_145837	Il17d	-0.602134321	0.079643046
NM_145826	Il17re	-0.951561482	0.001347568

Table 3: The log2-FCs changes of interleukin-related genes in GSE70437.

The genes IL-17 receptor A and IL-2 are up-regulated but IL-17 receptor E and D are down-regulated. We could not observe any significant change for IL-6.

We proceed to investigate the progress level of metabolic syndrome in the frame work of gene expression. The first data was provided by Hardy [18] with accession number GSE15773. The subcutaneous adipose tissues were taken from a body mass index (BMI)-matched, morbidly-obese cohort of patients that are either insulin-sensitive or insulin-resistant. Their experiment was intended to search mechanisms underlying obesity-related insulin resistance independent of BMI. Samples of gene expression data included 9 insulin-resistant, 10 insulin-sensitive patients.

We calculated log2-FCs for all genes using matrix data in GEO by software "limma", and extracted the results of interleukins. The results are shown in Table 4. In this table, we observe significant up-regulated expression of interleukin 6 (IL-6) (Table 4).

ID	Symbol	log_2fc	pvalues
205207_at	IL6	1.617607111	0.10771537
205067_at	IL1B	0.535385222	0.090357533
39402_at	IL1B	0.477463	0.104258714
205291_at	IL2RB	0.439009556	0.061264807
207433_at	IL10	0.404526	0.042629629
237753_at	IL21R	0.331073222	0.004112
237046_x_at	IL34	0.325022556	0.107305361
206148_at	IL3RA	0.317233444	0.026917949
204773_at	IL11RA	-0.327536556	0.004133575
206693_at	IL7	-0.635262556	0.027703301
227997_at	IL17RD	-0.647857	0.077271195

Table 4: The log2-FCs changes of interleukin-related genes in GSE15773.

The next sample of gene expression data was provided by Kim [19] with accession number GSE65557. They used adipose tissues taken from epididymis of C57BL/6J males fed a 60% high fat diet for up to 7 days to induce early obesity. We used samples of mice fed for 7 days

and 0 days for our calculation. Since the value type is count data, DESeq2 was utilized for computation of log2-FCs. The results are shown in Table 5, where a slight up-regulation of interleukin 15 and 6 receptor subunit alpha is observed. The function of interleukin 15 was already explained in the case of Plaisier (Table 5).

ID	Symbol	log_2fc	pvalues
10469289	Il15ra	0.448785064	3.56E-07
10499655	Il6ra	0.368753347	0.002656037
10415636	Il17d	-0.315482028	0.019175601
10606016	Il2rg	-0.402133186	0.00280747

Table 5: The log2-FCs changes of interleukin-related genes in GSE65557.

The final data is provided by Kobori [20] with GEO accession number GSE71367. Their original purpose was to examine the effect of quercetin on the gene expression and function of epididymal adipose tissue in Western diet-induced obese mice. They supplied 27 samples of expression data, but we did not use the 9 datasets with quercetin effect among these 27 samples, but used remaining the 18 datasets including 9 Western diet-induced obese mice and 9 datasets without fat diet (as control). We extracted 18 raw datasets from the GEO (9 fat and 9 control). The normalization and the calculation of log2-FCs were performed from these raw data using package "limma". The results are shown in (Table 6).

ID	Symbol	log_2fc	pvalues
1448575_at	Il7r	2.880956064	3.33E-07
1422177_at	Il13ra2	2.706745636	7.10E-08
1448576_at	Il7r	2.568433427	9.82E-07
1451798_at	Il1rn	2.26279329	3.42E-08
1423017_a_at	Il1rn	1.311385761	1.80E-08
1425663_at	Il1rn	1.250911315	3.46E-07
1436802_at	Ilf3	-0.402125718	2.62E-05
1426566_s_at	Il17re	-0.441242884	0.00931023
1420678_a_at	Il17rb	-0.444414853	0.002654742
1423276_at	Ildr1	-0.679141809	0.063921269

Table 6: The log2-FCs changes of interleukin-related genes in GSE71367.

Table 6 shows interleukins 7, 13, 1, 10 were up-regulated but interleukins 17 and 6 (signal transducer) were down-regulated.

The analysis of gene expression data was performed to estimate simultaneously the effects of meteorological factors and to speculate about the mechanisms connecting weather changes and the onset of disease. We extracted from the database GEO six datasets, where three datasets were used to estimate the effects of cold exposure and other three datasets were used to evaluate the influence of obesity or insulin resistance. In most cases, up-regulation of genes related to interleukins IL-1, IL-6 and IL-17 was observed, although the data of accession number GSE71367 (supplied by Kobori) showed different results compared with other data.

Discussion

The influences of weather on the onset of stroke and ischemic heart disease were studied mostly by linear regression models [1,2] and recently by hidden Marokov models [3,4]. The effects of obesity and metabolic syndrome were also discussed as an important factor for the incidences of these diseases [5,6].

If there is a common barometer indicating the effects of both weather and obesity, it will contribute to the prevention of these diseases. Gene expression analysis was suggested as a possible candidate for this indicator [8,9]. The gene expression data may be expected to reflect the effects of weather and metabolic syndrome and can be a possible stage or measure to argue these influences together. We explored, in the present work, the "gene bank" GEO and performed the calculation of log2-FC (log2FC) to these gene expression data.

We focused on the genes of interleukins, a group of cytokines, because a cytokine network was suggested as a bridge that connected the effects of weather and obesity [11]. There are reports that identified the effect of weather on cytokines [10]. On the other hand, obese individuals express more tumor necrosis factor alpha (TNF-alpha) mRNA and protein in fat tissue relative to the lean controls [5,6], and the increase in TNF-alpha induces interleukin-8 (IL-8) and interleukin-6 (IL-6) gene expressions [7].

We calculated log2-FCs of gene expression data extracted from the GEO with accession number GSE13432, GSE40486, GSE70437, GSE15773, GSE65557, GSE71367. The results of log2-FCs for the former three datasets are shown in Tables 1-3 measuring the effects by cold exposure. The up-regulated genes are IL-6st, IL-17re (in GSE13432), IL-15, IL-17rb (in GSE40486), IL-2rg, IL-17ra, IL-1rn, IL-15 (in GSE70437). The down-regulated genes are IL-7, IL-13 (in GSE13432), IL-f3(in GSE40486).

With respect to cold exposure, increases of the expression of genes related to IL-6 and IL-17 are significantly observed among three datasets. IL-6 and IL-17 are important interleukins for regulation of inflammatory reactions. Interleukin 6 (IL-6) plays a key role in the production of acute phase proteins. IL-6 dictates the transition from acute to chronic inflammation by changing the nature of leucocyte infiltrate and regulate chronic inflammatory responses. IL-6, in combination with IL-17, forms a cascade of positive feedback and induces rheumatoid arthritis and other chronic inflammatory diseases.

As for the effects of obesity or insulin resistance, the up-regulated genes are IL-6 (GSE15773), IL-15, IL-6ra (GSE65557), IL-7r, IL-13, IL-7, IL-1 (GSE71367). The down-regulated genes are IL-17rb, IL-f3 (GSE71367). Here an increase of gene expression related to IL-6 was observed. The decrease of genes related to IL-17 is observed for Kobori's data, which contradicts slightly the other results (Figure 1).

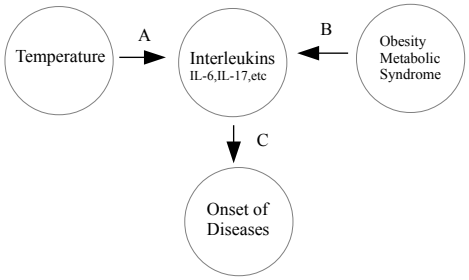

Figure 1: Decrease of genes related to IL-17 is observed for Kobori's data.

As a result, the significant changes of interleukins, especially IL-6, are observed as the effects of both cold exposure and obesity. The schematic picture is drawn in Figure 1, illustrating the roles of each factor, "cold exposure", "metabolic syndrome", "the onset of diseases", and "interleukins". Here we observe that interleukins play a role as bridge connecting all the other factors.

The arrow A in Figure 1 represents the effect of cold exposure on interleukins. The effects of weather on cytokines were reported by several others. Significant increases in the concentration of IL-6 were found due to cold exposure [21]. Temperature was associated with the methylation of intercellular adhesion molecule 1 (ICAM-1) [10]. An increase in VEGF was reported in cold-induced angiogenesis in adipose tissues [13].

The arrow B means the effect of obesity on interleukins. Obese patients show more tumor necrosis factor alpha (TNF-alpha) mRNA and protein in fat tissues compared with the lean individuals [5,6]. TNF-alpha is known to lead to insulin resistance [6]. TNF-alpha also plays an important role in inflammatory reactions. The increase in TNF-alpha induces IL-8 and IL-6 gene expressions [7].

The arrow C connects the interleukins and the onset of several diseases such as cerebral infarction and ischemic heart diseases. On the surface of fibroblasts, the expression of adhesion molecules such as intercellular adhesion molecule-1(ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are associated with up-regulation of interleukins, IL-6, IL-8 and IL-1a [7]. Thus these cytokines may lead to the onset of cerebral infarction and myocardial infarction.

Figure 1 suggests a mechanism in which interleukins perform a central role in connecting three factors: (1) weather, (2) obesity and (3) the incidence of diseases such as stroke and ischemic heart diseases. Figure 1 suggests that interleukins, including IL-6, supply a common stage to measure the effects of cold exposure and obesity on human health simultaneously.

Conclusion

To investigate a common measure of the effects of cold exposure and obesity, we examined the gene expression of interleukins based on the data in the database GEO and found an increase of interleukin-related genes which play an important role in inflammatory reactions. We can conclude that interleukins, including IL-6, can be a candidate of common indicators for the effects of both weather and obesity on human health. Our findings, together with a recent supply of simple kits to measure interleukins, may contribute to making a system to reduce the onset of diseases including stroke and ischemic heart diseases.

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