The Inflammatory Response in Acyl-CoA Oxidase 1 Deficiency (Pseudoneonatal Adrenoleukodystrophy)

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Abstract

Among several peroxisomal neurodegenerative disorders, the pseudoneonatal adrenoleukodystrophy(P-NALD) is characterized by the acyl-coenzymeAoxidase 1 (ACOX1) deficiency, which leadsto the accumulation of very-long-chain fatty acids (VLCFA) and inflammatory demyelination. However,the components of this inflammatory process in P-NALD remain elusive. In this study, we usedtranscriptomic profiling and PCR array analyses to explore inflammatory gene expression in patientfibroblasts. Our results show the activation of IL-1 inflammatory pathway accompanied by theincreased secretion of two IL-1 target genes, IL-6 and IL-8 cytokines. Human fibroblasts exposed tovery-long-chain fatty acids exhibited increased mRNA expression of IL-1alpha and IL-1beta cytokines.Furthermore, expression of IL-6 and IL-8 cytokines in patient fibroblasts was down-regulated byMAPK, p38MAPK, and Jun N-terminal kinase inhibitors. Thus, the absence of acyl-coenzyme A oxidase 1 activity in P-NALD fibroblasts triggers an inflammatory process, in which the IL-1 pathwayseems to be central. The use of specific kinase inhibitors may permit the modulation of the enhanced
inflammatory status.

Introduction

In several peroxisomal disorders, the peroxisomal fatty acid beta-oxidation pathway is defective. This may be dueto the specific deficiency of an enzyme or transporter involved in peroxisomal beta-oxidation or the absence of thecomplete organelle resulting from a genetic defect in oneof the many genes required for proper peroxisome biogenesisand maintenance (1, 2). Pseudoneonatal adrenoleukodystrophy(P-NALD) (OMIM 264470) is a rare,neuroinflammatory, and a neurodegenerative peroxisomal
disorder characterized by craniofacial dysmorphia,generalized hypotonia, hepatomegaly, infantile seizures,loss of motor achievements, and white matter demyelination(3– 6). P-NALD disease is due to acyl-coenzyme A(CoA) oxidase 1 (ACOX1) deficiency, which leads to aselective impairment of the peroxisomal fatty acid beta-oxidationpathway specifically affecting the oxidation ofvery-long-chain fatty acids

(VLCFA). As a consequence,VLCFA accumulate in plasma and tissues (1, 7). ACOX1 catalyzes the alpha, beta-dehydrogenation of a range of acyl-CoAesters, including the CoA-esters of dicarboxylic acids, eicosanoidderivatives, and saturated VLCFA (2, 7, 8). In human and mice, the ACOX1 enzyme is encoded by asingle gene, which generates two splice variants, includingexon 3a or exon 3b, respectively, leading to the synthesisof two protein isoforms ACOX1a or ACOX1b (2, 9). Althoughno apparent genotype-phenotype correlation hasbeen established in P-NALD (7), a patient with a singlehomozygous mutation on exon 3b has also the clinicalsigns and symptoms of P-NALD (10), thus revealing thesubstrate specificity of the specific ACOX1 isoforms (2,8). Mice lacking Acox1 manifest severe inflammatory steatohepatitiswith increased intrahepatic H_2O_2 levels andhepatocellular regeneration (11, 12). Progressively,chronic endoplasmic reticulum stress contributes to hepatocarcinogenesis(13), and this steatoticACOX1null phénotype can be reversed by expression of the humanACOX1b isoform (8, 13). However, even if they showsmaller size and growth retardation when compared withtheir littermates, Acox1 null mice have no apparent neurologicaldisorder (11, 14). In brain lesions of patientsdeveloping the demyelinating form of peroxisomalX-linked adrenoleukodystrophy, oxidative, inflammatory,and apoptotic processes have been described (15–17). In this related peroxisomal disorder, lipid dérivatives with an abnormally high proportion of VLCFA residueshave been proposed to trigger the initial cascade of theinflammatory demyelination (18, 19). However, the componentsof this inflammatory process in P-NALD haveremained elusive. To explore the inflammatory responsein ACOX1 deficiency, we used two patient-derived fibroblastsfor transcriptomic microarray analysis associatedwith a PCR array screening in an attempt to identify theinvolved proinflammatory components.

In the present work, we report the expression profilingof inflammatory cytokines in fibroblasts from P-NALDpatients. Alterations in the expression of IL-1 pathwaywere revealed and accompanied by increased secretions ofthe IL-6 and IL-8. Fibroblasts exposed to VLCFA showincreased expression of cytokines mRNA. Signaling pathwaysinvolved in the induction of these cytokines were alsoexplored.

Materials and Methods

Cell culture and VLCFA treatment

Skin fibroblasts were cultured as described (7) and handledaccording to national and institutional guidelines. Cerotic acid(C26:0) (Sigma-Aldrich, St. Louis, MO) was solubilized in alpha-cyclodextrine(Sigma-Aldrich). Final concentration of alpha-cyclodextrine(vehicle) in the culturemediumwas 1 mg/ml. For fibroblaststreatment, the final concentration of C26:0 was 10 microM.

Acyl-CoA oxidase activity measurement

It was performed as described by Oaxaca-Castillo et al. (2).

Immunostaining, fluorescence microscopy, and Nile red staining

Immunostaining, fluorescence microscopy, and Nile redstaining were achieved as previously described (20).

Microarray analysis (Affymetrix, Santa Clara, CA), cytokinesanalysis by Cytometric Bead Array Human Inflammation kit (BDBiosciences, Courtaboeuf, France), andPCRarray analysis (PAHS-011; SABiosciences-QIAGEN, Courtaboeuf, France) are describedin

Supplemental Materials and Methods, published on The EndocrineSociety's Journals Online web site at http://endo.endojournals.org

Results and Discussion

Characterization of patient-derived-deficient fibroblasts

To characterize the deficiency of ACOX1 in P-NALDfibroblasts, the activity of ACOX1 was first measured incell extracts. As shown in Fig. 1A, weak residual palmitoyl-CoA oxidase specific activity was present in patient 1fibroblasts, although much reduced, whereas thisACOX1activity was undetectable in patient 2 fibroblasts. Bothpatients' fibroblast cells exhibited a strong reduction in thenumber of peroxisomes per cell, as shown by peroxisomesimmunostaining with antibodies against catalase (matrixprotein) and 70-kDa peroxisomal integral membrane protein(Fig. 1B). This is accompanied by the enlarged size ofperoxisomes as shown by anticatalase immunofluorescence(Fig. 1C). Fibroblasts Nile red staining reveals atransition from the predominance of polar lipids in controlfibroblasts (green fluorescence) (Fig. 1C) to an accumulationof neutral lipids in P-NALD fibroblasts (yellow fluorescence)(Fig. 1C). Accumulation of VLCFA in plasmahas been previously shown for these patients (7).

Transcriptomic profiling of inflammatory genes inP-NALD fibroblasts

To identify proinflammatory genes that are dysregulatedin P-NALD/ACOX1-deficient fibroblasts, we usedAffymetrix microarray profiling. Transcriptional profilingrevealed that a number of genes coding for cytokinesand other proinflammatory proteins was up-regulated (≥1.5), including, IL-6, IL-8, and several TNFalpha familymembers (3, 8, 9, 10A, 12, and 14) as well as interferoninducibleproteins (Supplemental Table 1). Interestingly,the expression of genes coding for cytokines IL-6, IL-8, and TNFalpha, which are typically produced by macrophages and by CD4+ T cells Th1, has also been found to beincreased in multiple sclerosis and cerebral forms of Xadrenoleukodystrophylesions (15). On the other hand,several cytokines and chemokine mRNA are stronglydown-regulated in P-NALD fibroblasts, including chemokine(C-X-C motif) ligand (CXCL)14 andCXCL12genes,which have been shown to participate in the regulation ofcell or tissues homeostasis (21, 22).

Alterations of the IL-1beta pathway in P-NALD fibroblasts

To define a specific inflammatory pathway activated inACOX1 deficiency, PCR array (SABiosciences), containing84 key genes mediating the inflammatory response andwhich include several genes deregulated in our transcriptomicprofiling, was used to determine the profile of reverse-transcribed RNA from the two patients derived fibroblastscompared with the control fibroblasts. Table 1shows results for genes significantly regulated in both patients.Based on the $2^{-\Delta\Delta CT}$ analyses of three PCR arrays(n=3) for each fibroblasts sample, 14 genes were strikinglyand similarly regulated in ACOX1-deficient fibroblastsfor both patients (cut-offs, -1.5-fold ≥ gene fold expression ≥1.5-fold). Absence of ACOX1 activity,which leads to VLCFA accumulation, triggered mRNAup-regulation of IL-1, IL-1, IL-1R1, IL-1RN, IL-17C,secreted phosphoprotein 1 (SPP1), chemokine (C-C motif)receptor type 1 (CCR1), chemokine (C-C motif) ligand(CCL)3, CCL7, CAAT/enhancer binding protein (CEBP), and Toll-

interacting protein (TOLLIP) (1.65- to15-fold) and down-regulation of CXCL14, CCL26, andCXCL5 (1.92- to 50-fold). Remarkably, all these regulatedgenes are connected to the IL-1 pathway. Activationof this pathway is triggered by the binding of theIL-1/IL-1 heterodimer to IL-1R1 (23). Correspondingly,Table 1 shows that IL-1, IL-1, and IL-1R1mRNAare significantly induced in P-NALD fibroblasts. Thus,IL-1, which is recognized as a proinflammatory cytokine(24), is known to control the expression of other inflammatorygenes, including TNF and interferon through awell-defined transduction signaling pathway (24). In-triguingly, the expression of IL 1RN, an IL-1 receptor antagonist,which modulates the inflammatory responses(23), was induced as well (Table 1). It is noteworthy thatIL-1RN is also induced in patient serum developing a neurologicaldisorder, such as schizophrenia (25). We cannotexclude that IL-1RN induction may contribute to the atténuation of the inflammatory stress during P-NALD progressionby antagonizing IL-1 activity and thus preservingimmune homeostasis (23). Furthermore, another cytokinetranscript IL-17C was increased more than 2-fold in bothpatients derived fibroblasts (Table 1). It is a homologuegene of IL-17, which is increased in autoimmune diseases,such as multiple sclerosis (26). Thus, IL-17C may participates in P-NALD-fibroblasts to the release of both IL-1and TNF (27).

As shown in Table 1, the SPP1 (also called osteopontin)mRNA is highly induced (at least 4-fold) in ACOX1-nullfibroblasts. Reportedly, SPP1 expression is induced byIL-1 or IL-1 as well (28, 29). SPP1 is an extracellularglycoprotein, belonging to the integrin superfamily (30).

This two-sided mediator acts in a context-dependent manneras a neuroprotectant (31) or as triggering the neuronaltoxicity (32) and has been reported in several neurodegenerativediseases, such as multiple sclerosis, Parkinson'sdisease, and Alzheimer's disease (32). Interestingly, in PNALDfibroblasts beside the induction of cytokinemRNA, the expression of several chemokine transcripts(CCL3, CCL7, CCL26, CCR1, CXCL5, and CXCL14) isstrongly modified as well (Table 1). Transcripts of bothCCR1 and its chemokine ligands CCL3 (Rantes/macrophageinflammatory protein 1) and CCL7 (monocytechemoattractant protein-3) were highly induced inP-NALD fibroblasts. CCR1 and its ligands play a criticalrole in the recruitment of inflammatory cells to neurologicallesions (33, 34). Hence, infusions of several cell lineswith IL-1 or IL-1, including Caco-2, hepatoma, smoothmuscle, or astrocytes cell lines (35–38), display enhancedsynthesis of CCL3 and/or CCL7, which may interact withits CCR1 receptor. Thus, induction of CCR1 and its ligandsin P-NALD-fibroblasts may reflect a common inflammatoryresponse as reported in many neurodegenerativediseases (34, 39).

Interestingly, the increased expression of CEBP(2.25-fold) and TOLLIP (mean 2.8-fold) constitutes an additionalargument of the activation of the IL-1 inflammatorypathway in P-NALD-fibroblasts (Table 1 and SupplementalTable 1). Hence, enhanced synthesis of CCL3 ligand(Table 1) through the activation IL-1 pathway (as citedabove) is dependent on the transcriptional activation ofCCL3 gene promoter by CEBP (40). Furthermore, TOLLIPwhich constitutes an important component of IL-1Rsignaling pathway (41), can limit the production of proinflammatorycytokines (42) by controlling the magnitudeof IL-6 and TNF in response to IL-1beta (43).

According to our transcriptomic profiling results (SupplementalTable 1) and using cytometric bead array analysis,we show in Fig. 2 that the secretions of IL-6 and IL-8cytokines were strongly induced in P-NALD fibroblasts,whereas secretion of TNF was not significantly changed(data not shown). Thus, ACOX1 deficiency in P-NALDfibroblasts leads to the activation of IL-1 inflammatorypathway and enhanced synthesis of its target genes, IL-6and IL-8 (Fig. 2).

From the 84 genes present in PCR array, only threechemokine genes (i.e. CCL26, CXCL5, and CXCL14) exhibiteda similar down-regulation in the two patients derivedfibroblasts (Table 1). The CCL26 (or Eotaxin-3) is astrikingly decreased chemokine gene in P-NALD-fibroblasts(3.5- to 14-fold) (Table 1). This may be correlatedto the induction of CCL3, revealing an autocrinemechanism involving CCL3, which selectively down-regulatesCCL26 (44). Two other transcripts encodingchemokine ligands were highly decreased in P-NALD fibroblasts,and both belong to the CXCL family. CXCL5(also called epithelial-derived neutrophil-activating peptide78) is down-regulated in P-NALD fibroblasts (Table1) and also in plasma of patients with chronic liver diseaseand serves as biomarker of necroinflammation and liverfibrosis (45). Hence, P-NALD patients are known to develophepatomegaly and liver fibrosis (7). AlthoughCXCL14 deficiency has been linked to the attenuation ofobesity and brain control of behavior feeding (46). Decreasedexpression of both CXCL5 and CXCL14 (Table1) may reflect the dysregulation of lipid metabolism, thusimpacting the inflammatory process during P-NALD diseaseprogression.

Inflammatory response of fibroblasts to increasedVLCFA-cerotic acid concentration

The increase in the VLCFA levels precede largely thewhite matter demyelination in P-NALD and the neuroinflammatoryresponse in childhood X-linked adrenoleukodystrophyas well (15, 18, 19). Although it is wellknown that both P-NALD and X-linked adrenoleukodystrophyare associated with the accumulation ofVLCFA(1,8), the direct role of VLCFA in the induction of inflammatory process still is, however, merely speculative (18).To try and understand this possible relationship, wetreated control fibroblasts with the cerotic C26:0 fattyacid. Figure 3 shows the time-course expression of cytokines(IL-1alpha, IL-1beta, and IL-6) and ACOX1b, the ACOX1isoform involved in C26:0-beta-oxidation (2, 8), transcriptsin fibroblasts exposed to 10 microM C26:0 during 48 h. Asshown in Fig. 3, enhanced cytokines mRNA expression,particularly IL-1alpha and IL-1beta, was evident already between6 and 12 h, showing a sequential and similar inductionwith a maximum at 12 h. A return to the control level ofboth cytokine mRNA at 18 h is concomitant to a delayedACOX1b mRNA expression hit (Fig. 3). By contrast, 6 hlater (a 24-h time course), the expression levels of IL-1alpha andIL-1beta mRNA increased at 24 and 48 h, whereas at the opposite,ACOX1 transcripts were reduced again and stay Under the control threshold at 48 h ofVLCFAtreatment. Thus,C26:0-VLCFA seems to regulate concomitantly and sequentially,in a divergent manner, both cytokines and ACOX1mRNA levels. This sequential regulation in fibroblasts isprobably linked to the fact that cytokines, such IL-1beta, areable to increase accumulation of VLCFA through inhibitionof the peroxisomal beta-oxidation of C26:0-cerotic acid by anunknown mechanism (19). This may install a vicious circle,in which C26:0 fatty acid triggers earlier increase of mRNAcytokines, which down-regulate peroxisomal beta-oxidationleading to the accumulation of VLCFA. The latter in turnpromotes the reinduction of cytokine transcripts during asecond late phase.

Signaling pathway involved in cytokines expression

To explore the transduced signaling associated with IL-1pathway activation in P-NALD fibroblasts, we used severalknown kinase inhibitors and evaluate by cytometry the level of both IL-6 and IL-8 cytokines. In the light of the activationof IL-1 pathway in P-NALD/ACOX1-deficient fibroblasts,induced IL-6 is mostly addressed to themedium(Fig. 4A). Byusing PD 98059, a selective noncompetitive inhibitor of theMAPK kinase

(MAPKK), we have shown the inhibition ofsecreted IL-6. This result was confirmed by P-NALD fibroblasts exposure to another MAPKK inhibitor, U0126 (Fig.4A). Likewise, SB 203580, a highly specific inhibitor of p38MAPKK, decreased IL-6 secretion as well. Similarly, PD98059, U0126, and SB 203580 molecules inhibited IL-8 expressionin P-NALD fibroblasts (Fig. 4). On the other hand,treatment with SP600125 compound, a selective Jun kinases(JNK) inhibitor, exhibited differential effects on IL-6 andIL-8 secretions by decreasing only IL-8 secretion (Fig. 4, AandB).Regardingthe activation of IL-1pathwayinP-NALDfibroblasts, the induction of IL-8 seems to be dependent onthe activation of p38MAPK and JNK kinase.
Hence, IL-1 transduction cascadethrough these kinases has beenshownforbothIL-8andCCL3(47). In addition, theimplication of nuclear factor KBsignalingpathway is not excluded, becauseC/EBPbeta-dependent transcriptional inductionof chemokines by IL-1 is triggeredthrough the activation of p38MAPK and inhibitor of KB kinase (40).
Accordingly, we also reported (SupplementalTable 1) that themRNAincreaseof TNF receptor-associated factor 6,which is known as an IL-1 control relay,functions as signal transducer of inhibitorof KB kinase (48).

Conclusions
Although precise role of VLCFA accumulationin P-NALD demyelination remainsto be determined, their ability toinduce an inflammatory response addsfurther evidence to the role of peroxisomalbeta-oxidation in the maintenanceof cellular homeostasis. Therefore, thereported results in the present reporthighlight that in P-NALD, ACOX1 deficiencyis associated with significantalterations in the inflammatory responseleading to the activation of IL-1pathway. Such activation is triggeringthe induction of both IL-6 and IL-8 cytokinesmostly throughMAPKand p38MAPKK, in addition to the possiblerole of JNK kinase in IL-8 induction.
Our results also suggested a feed-forwardmechanism leading to an additionaldown-regulation of peroxisomalVLCFA beta-oxidation by the producedcytokines, which may aggravates theinflammatory picture in P-NALD.
These results open a way to explore the modulation ofkinase pathway in an attempt to reduce the inflammatoryprocess in this orphan disease.

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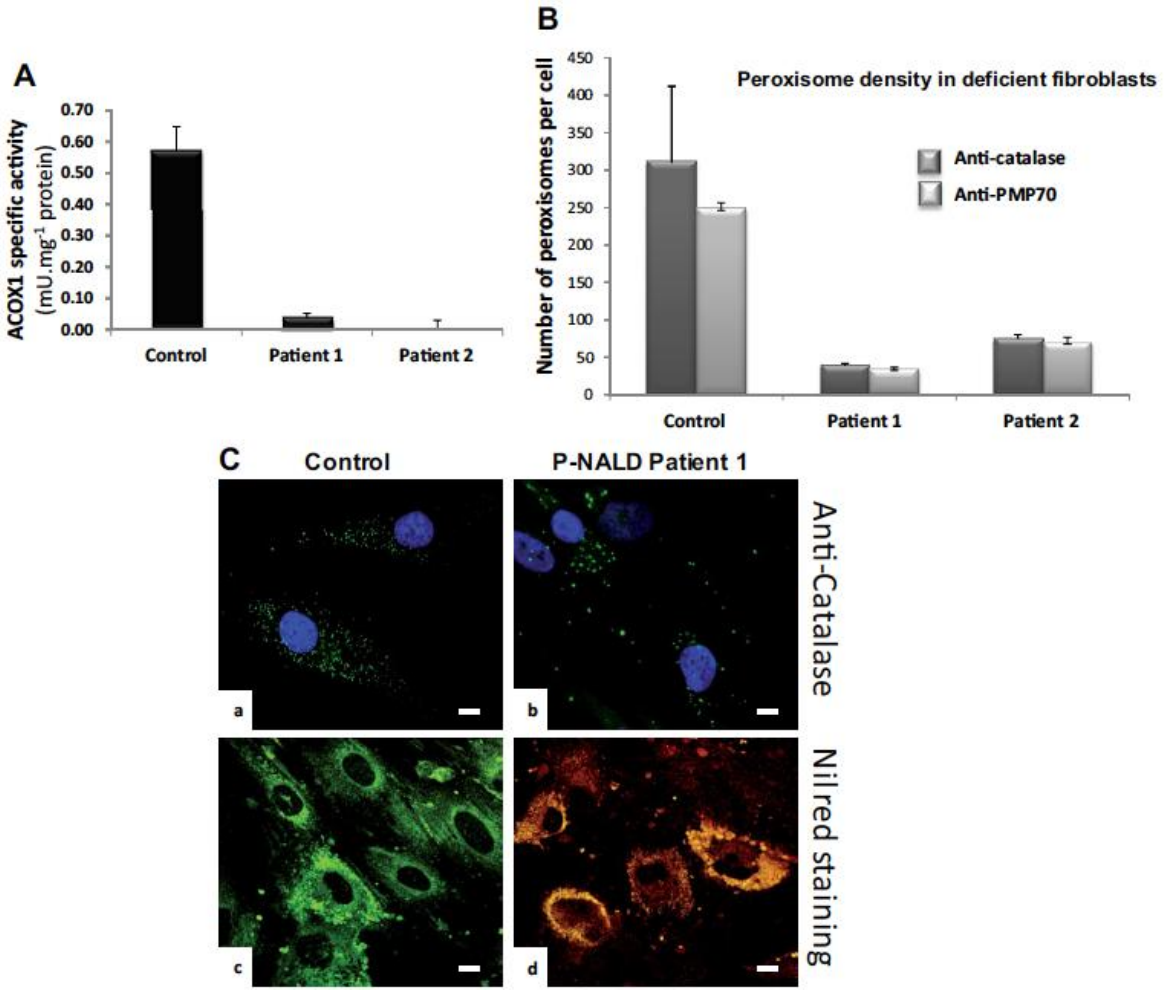
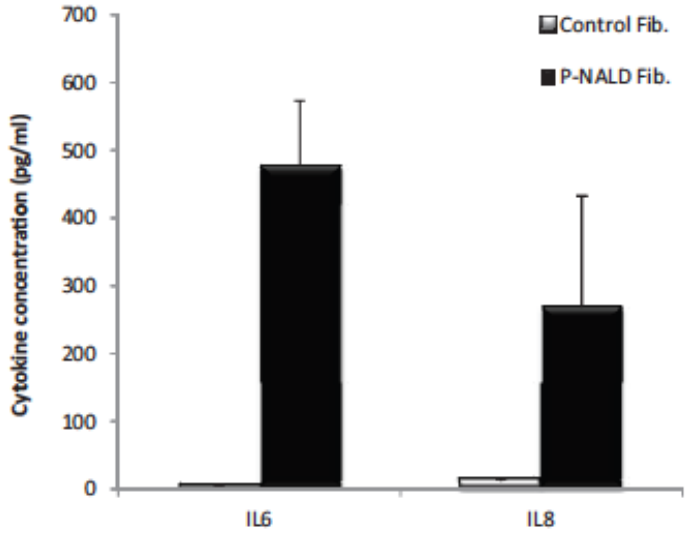
Figures



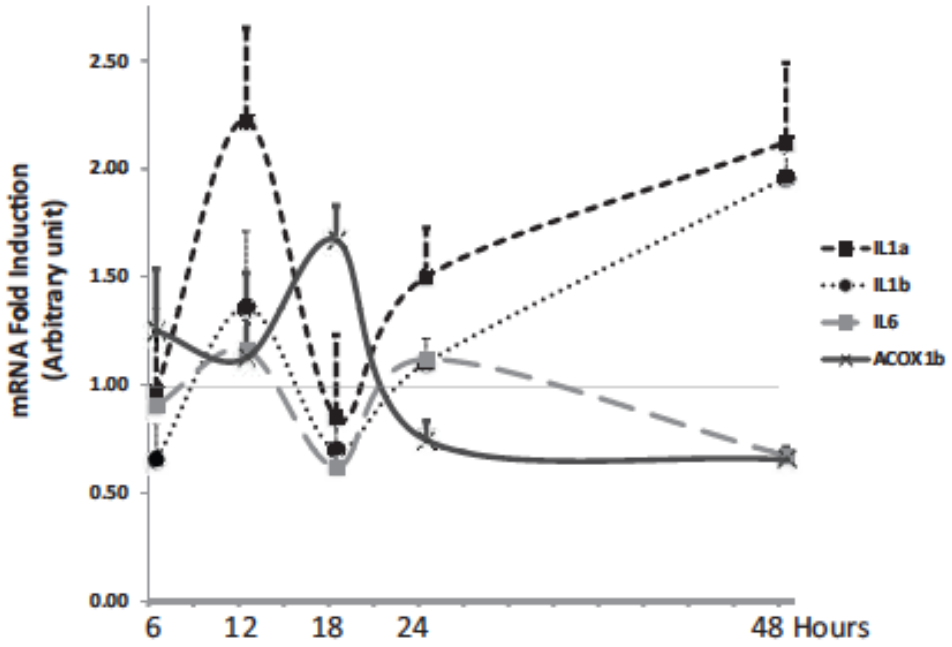
El Hajj, Figure 1

Characterization of P-NALD patient's fibroblasts. A, ACOX1 activity measured in both patients' (1 and 2) fibroblasts. Enzymatic activity ofACOX1 was measured using palmitoyl-CoA as substrate (2). B, Immunostaining of fibroblasts (control, patient 1 and patient 2 fibroblasts) bycatalase, a peroxisomal marker, reveals high number of peroxisomes in control cells and low number of peroxisome in P-NALD patient 1 fibroblasts. C, Immunostaining of control (a) and P-NALD (b) fibroblasts by anticatalase reveals enlarged peroxisome size in patient 1 P-NALDfibroblasts (b). Nile red staining of control (c) and P-NALD (d) fibroblasts. The green color indicates the predominance of polar lipids in control cells,whereas the yellow staining of deficient fibroblasts reveals an accumulation of neutral lipids. Microscope images magnifications, X100. Scale bar,10 μm. PMP70, 70-kDa peroxisomal integral membrane protein.



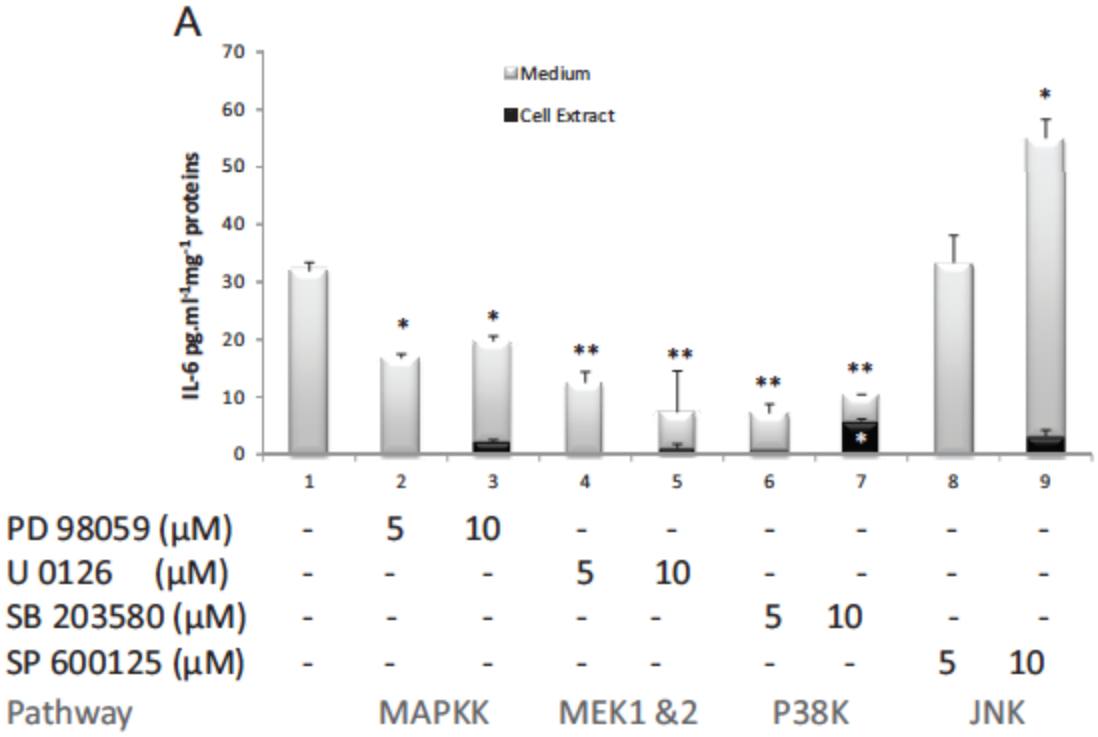
El Hajj, Figure 2

IL-6 and IL-8 cytokine secretion in the culture mediumobtained from the control and P-NALD fibroblasts. 1.2 x 10^6 cellswere seeded in 10-cm Petri dishes and cultured in DMEMsupplemented with 10% fetal calf serum at 37 C with 5% CO2; 24 hafter seeding, fibroblasts were rinsed three times with PBS andincubated in DMEM without serum for 18 h. Culture media werecollected and analyzed by cytometric bead array as described in Materials and Methods. Values are mean ± SD. Fib, Fibroblasts.



El Hajj, Figure 3

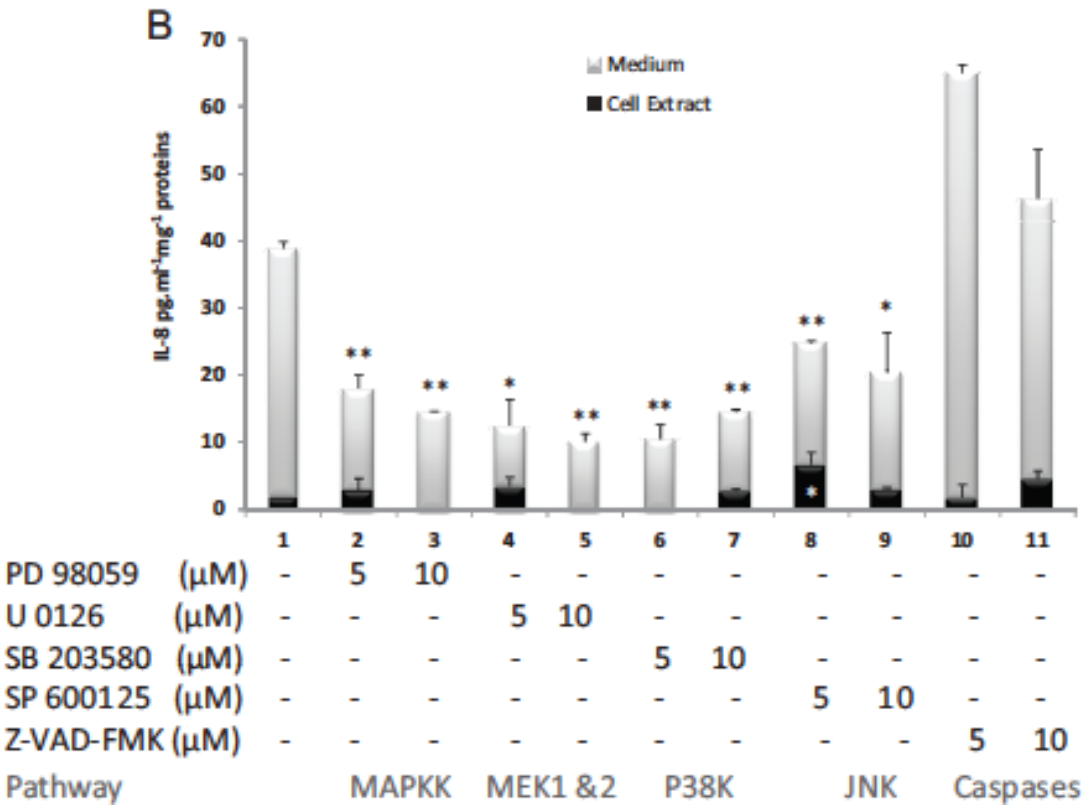
Time-course fold inductions of cytokines and ACOX1b mRNAin human control fibroblasts treated with C26:0 at 10 μM in α-cyclodextrine at final concentration of 1 mg/ml. 1.2 x 106 cells wereseeded in 10-cm Petri dishes and cultured in DMEM complementedwith 10% fetal calf serum at 37 C with 5% CO2; 24 h after seeding,fibroblasts were rinsed three times with PBS solution and incubated in DMEM with α-cyclodextrine (1 mg/ml) as control or with α-cyclodextrine (1 mg/ml) supplemented with C26:0 at 10 μM. Cellswere collected at the indicated time point by trypsination. Values are mean ± SD. Total RNA isolated from treated fibroblasts were analyzedby RT-quantitative PCR using



El Hajj, Figure 4A

Regulation of IL-6 cytokine in P-NALD fibroblasts by kinases inhibitors.

P-NALD fibroblasts were treated with the indicated concentration of kinase inhibitors for 24 h.Culture media and fibroblasts were collected separately. Cells were washed in PBS solution. Themedia and the cell pellet were deep frozen at -80 C until analysis. Values are mean ± SD.Statistical significance of higher mean signal intensity (**, $P < 0.01$; *, $P < 0.05$) compared withthe control. MEK, MAP kinase or extracellular signal-reregulated kinase.



Hajj, Figure 4B

Regulation of IL-8cytokine in P-NALD fibroblasts by kinases inhibitors.

P-NALD fibroblasts were treated with the indicated concentration of kinase inhibitors for 24 h.Culture media and fibroblasts were collected separately. Cells were washed in PBS solution. Themedia and the cell pellet were deep frozen at -80 C until analysis. Values are mean ± SD.Statistical significance of higher mean signal intensity (**, $P < 0.01$; *, $P < 0.05$) compared withthe control. MEK, MAP kinase or extracellular signal-reregulated kinase.

TABLE 1. PCR array analysis of genes encoding inflammatory cytokines in P-NALD fibroblasts as compared to the control

Gene symbol	Gene name	Fold induction Patient 1	Fold induction Patient 2
IL1A	IL-1α	5.50[c]	5.58[b]
IL1B	IL-1β	1.65[a]	3.60[b]
IL17C	IL-17C	2.39[a]	2.54[a]
IL1R1	IL-1 receptor type I	2.18[c]	2.43[b]
IL1RN	IL-1 receptor antagonist	1.54[a]	3.02[b]
SPP1	Secreted phosphoprotein 1 (osteopontin)	3.98[c]	7.89[c]
CCR1	Chemokine (C-C motif) receptor 1	6.18[c]	2.60
CCL3	Chemokine (C-C motif) ligand 3	10.27[c]	2.49[a]
CCL7	Chemokine (C-C motif) ligand 7	14.19[b]	15.24[b]
CXCL14	Chemokine (C-X-C motif) ligand 14	−5.26[c]	−1.92[b]
CCL26	Chemokine (C-C motif) ligand 26	−14.28[c]	−3.57[c]
CXCL5	Chemokine (C-X-C motif) ligand 5	−50[c]	−8.34[c]
TOLLIP	Toll-interacting protein	3.31[c]	2.32[b]
CEBPβ	CCAAT/enhancer binding protein, β	2.45[b]	2.07[a]

Values indicate fold change in P-NALD fibroblast obtained using the Excel analysis tool (SABiosciences), which includes descriptive statistics.

[a] $P < 0.1$.

[b] $P < 0.01$.

[c] $P < 0.001$.

Supplemental Table 1

Table 1: Microarray results of regulated inflammatory genes in P-NALD fibroblastsobtained by Affimetrix profiling. Genes were considered to be significantly changed whenraw q-value <0.05 and -1.2>fold-change >1.2.

Supplemental Material and Methods

Microarray analysis: Total RNA was extracted from fibroblasts as recommended by thesupplier (Qiagen, Courtaboeuf, France). RNA quality was measured on an Agilent 2100bioanalyzer (Agilent Technologies, Amsterdam, the Netherlands) using 6000 Nano Chips
according to manufacturer's instructions. cRNA synthesis was performed using 5 µg of RNAusing one cycle kit (Affymetrix, Santa Clara, CA). Hybridization, washing and scanning ofAffymetrix human genome 133 2.0 plus arrays was carried out according to standardAffymetrix protocols. Scans of the Affymetrix arrays were processed using packages from theR/Bioconductor project. Arrays were normalized with quantile normalization and expressionlevels of probe sets were calculated using the robust multichip average method. Differentiallyexpressed probe sets were identified using Limma and genes were considered to besignificantly changed when raw q-value <0.05 and -1.2>fold-change >1.2.

Cytokines analysis: Flow cytometric quantification of cytokine secretion with theCytometric Bead Array (CBA): Culture medium was collected by centrifugation and stored at−80° C. Samples were defrosted and centrifuged immediately before cytokine analysis. IL-8and IL-6 were quantified using the Cytometric Bead Array Human Inflammation kitaccording to the supplier instructions (BD Biosciences, Courtaboeuf, France).

PCR array analysis: total RNA was isolated as described above. cDNA synthesis andPCR arrays (PAHS-011) were achieved using the RT2 PCR Array First Strand kit and RT^{2}qPCR Master Mixes respectively (SABiosciences-Qiagen, Courtaboeuf, France). PCR arraysincluding customized primers for 84 key human genes mediating the inflammatory response,five housekeeping genes, 3 RT controls and 3 positive qPCR controls were performedaccording to the manufacturer's instructions in an iCycler (Bio-Rad, Marnes La Coquette,France). Data analysis was done using the excel analysis tool(www.sabiosciences.com/pcrarraydataanalysis.php), which includes descriptive statistics,including fold change and volcano plots.

gene name	accession	description	Fold Induction	Log10(X)
IL8	NM_000584	interleukin 8	16,49	1,22
TNFSF9	NM_003811	tumor necrosis factor (ligand) superfamily, member 9	12,35	1,09
CXCL2	M57731	chemokine (C-X-C motif) ligand 2	7,87	0,90
IL13RA2	NM_000640	interleukin 13 receptor, alpha 2	7,14	0,85
IL6	NM_000600	interleukin 6 (interferon, beta 2)	6,53	0,81
TNFRSF10A	W65310	tumor necrosis factor receptor superfamily, member 10a	4,97	0,70
CXCL1	NM_001511	chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)	4,67	0,67
CCL26	AF096296	chemokine (C-C motif) ligand 26	4,33	0,64
TNFAIP8	BC005352	tumor necrosis factor, alpha-induced protein 8	4,03	0,61
TNFAIP3	NM_006290	tumor necrosis factor, alpha-induced protein 3	3,44	0,54
IFI30	AK123477, BC	interferon, gamma-inducible protein 30	3,15	0,50
NFKBIZ	BE646573	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta	3,09	0,49
CCL8	AI400658, Y1	chemokine (C-C motif) ligand 8	2,93	0,47
TNFRSF10C	NM_003841	tumor necrosis factor receptor superfamily, member 10c, decoy without an intra	2,73	0,44
IFI6	NM_022873	interferon, alpha-inducible protein 6	2,63	0,42
NFKBIE	NM_004556	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsi	2,63	0,42
IL6ST	NM_002184	interleukin 6 signal transducer (gp130, oncostatin M receptor)	2,53	0,40
IL12A	BC035571	interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte ma	2,48	0,39
NFKBIA	AI078167	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alph	2,38	0,38
IFI30	NM_006332	interferon, gamma-inducible protein 30	2,30	0,36
IFIT1	NM_001548	interferon-induced protein with tetratricopeptide repeats 1	2,25	0,35
SOCS2	NM_003877	suppressor of cytokine signaling 2	2,21	0,34
IFI27	NM_005532	interferon, alpha-inducible protein 27	2,12	0,33
TNFRSF12A	NM_016639	tumor necrosis factor receptor superfamily, member 12A	2,07	0,32
IFIT3	AI075407	interferon-induced protein with tetratricopeptide repeats 3	2,06	0,31
TOLLIP	NM_019009	toll interacting protein	2,04	0,31
CXCL3	NM_002090,	chemokine (C-X-C motif) ligand 3	1,98	0,30
TNFRSF10D	AI738556	tumor necrosis factor receptor superfamily, member 10d, decoy with truncated	1,92	0,28
IL17RB	NM_018725	interleukin 17 receptor B	1,92	0,28
IFIT2	AA131041	interferon-induced protein with tetratricopeptide repeats 2	1,87	0,27
TNFAIP6	NM_007115	tumor necrosis factor, alpha-induced protein 6	1,79	0,25
IL32	NM_004221	interleukin 32	1,76	0,24
TNFSF7	NM_001252	tumor necrosis factor (ligand) superfamily, member 7	1,75	0,24
TNFRSF14	BC002794	tumor necrosis factor receptor superfamily, member 14 (herpesvirus entry medi	1,74	0,24
CCRL1	NM_178445	chemokine (C-C motif) receptor-like 1	1,73	0,24
IL1RAP	NM_002182	interleukin 1 receptor accessory protein	1,65	0,22
IL15	NM_000585	interleukin 15	1,62	0,21
IRAK3	NM_007199	interleukin-1 receptor-associated kinase 3	1,60	0,20
CXCL3	NM_002090	chemokine (C-X-C motif) ligand 3	1,56	0,19
SOCS5	NM_014011	suppressor of cytokine signaling 5	1,56	0,19
IFI44L	NM_006820	interferon-induced protein 44-like	1,53	0,19
IL24	AI084226	interleukin 24	1,53	0,19
TRAF6	NM_004620	TNF receptor-associated factor 6	1,52	0,18
IRAK2	AI246590	interleukin-1 receptor-associated kinase 2	1,49	0,17
IL10RB	BF526978	interleukin 10 receptor, beta	1,42	0,15
IL4R	NM_000418	interleukin 4 receptor	1,42	0,15
CCL18	Y13710	chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)	1,40	0,15
IFNA5	NM_002169	interferon, alpha 5	1,40	0,15
CCRL1	NM_178445	chemokine (C-C motif) receptor-like 1	1,40	0,15
CCL3	NM_002983	chemokine (C-C motif) ligand 3	1,38	0,14
IL6ST	AW242916	interleukin 6 signal transducer (gp130, oncostatin M receptor)	1,37	0,14
TNFRSF11A	AW026379	tumor necrosis factor receptor superfamily, member 11a, NFKB activator	1,36	0,13
IFI35	BC001356	interferon-induced protein 35	1,36	0,13
SOCS4	BF446961	suppressor of cytokine signaling 4	1,36	0,13
CCR8	NM_005201	chemokine (C-C motif) receptor 8	1,34	0,13
CXCL6	NM_002993	chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2)	1,34	0,13
TNFRSF18	AF241229	tumor necrosis factor receptor superfamily, member 18	1,33	0,12
IRAK1	NM_001569	interleukin-1 receptor-associated kinase 1	1,32	0,12
CXCL10	NM_001565	chemokine (C-X-C motif) ligand 10	1,30	0,11

IL12RB1	AI637915	interleukin 12 receptor, beta 1	1,28	0,11
CCL2	S69738	chemokine (C-C motif) ligand 2	1,28	0,11
IL1RL2	AF284434	interleukin 1 receptor-like 2	1,27	0,10
TNFRSF25	NM_003790	tumor necrosis factor receptor superfamily, member 25	1,27	0,10
TNFRSF13C	AF373846	tumor necrosis factor receptor superfamily, member 13C	1,27	0,10
IL9	BG398985	interleukin 9	1,27	0,10
IL27	BC062422	interleukin 27	1,26	0,10
TNFSF13	AF114012	tumor necrosis factor (ligand) superfamily, member 13	1,26	0,10
TNFAIP1	NM_021137	tumor necrosis factor, alpha-induced protein 1 (endothelial)	1,26	0,10
IL17RD	AU148326	interleukin 17 receptor D	1,25	0,10
TRAF2	NM_021138	TNF receptor-associated factor 2	1,25	0,10
IL1F7	AF200496	interleukin 1 family, member 7 (zeta)	1,25	0,10
CCR10	NM_016602	chemokine (C-C motif) receptor 10	1,24	0,09
IL1F10	NM_032556	interleukin 1 family, member 10 (theta)	1,23	0,09
TNFRSF10B	AF016266	tumor necrosis factor receptor superfamily, member 10b	1,23	0,09
IL18	NM_001562	interleukin 18 (interferon-gamma-inducing factor)	1,22	0,09
SOCS1	AB005043	suppressor of cytokine signaling 1	1,22	0,09
IFI44	NM_006417	interferon-induced protein 44	1,21	0,08
TRADD	L41690	TNFRSF1A-associated via death domain	1,21	0,08
IFNA1	NM_024013	interferon, alpha 1	1,21	0,08
TNFAIP8L1	BF338045	tumor necrosis factor, alpha-induced protein 8-like 1	1,21	0,08
CCL20	BC020698	chemokine (C-C motif) ligand 20	1,20	0,08
CCL4	NM_002984	chemokine (C-C motif) ligand 4	1,20	0,08
IFNB1	M28622	interferon, beta 1, fibroblast	1,19	0,08
CXCL11	BC012532	chemokine (C-X-C motif) ligand 11	1,19	0,08
IL1RAPL2	AJ272208	interleukin 1 receptor accessory protein-like 2	1,19	0,08
IL25	NM_022789	interleukin 25	1,18	0,07
NFKBIB	AA044140	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, beta	1,18	0,07
IFNA8	NM_002170	interferon, alpha 8	1,18	0,07
IL17RE	NM_153482	interleukin 17 receptor E	1,18	0,07
TRAP1	AW468509	TNF receptor-associated protein 1	1,18	0,07
ISG20L1	NM_022767	interferon stimulated exonuclease gene 20kDa-like 1	1,18	0,07
CCR5	NM_000579	chemokine (C-C motif) receptor 5	1,17	0,07
IFIH1	BC046208	interferon induced with helicase C domain 1	1,17	0,07
TNFSF15	NM_005118	tumor necrosis factor (ligand) superfamily, member 15	1,17	0,07
TNIP3	NM_024873	TNFAIP3 interacting protein 3	1,17	0,07
NFKB2	BC002844	nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)	1,17	0,07
IL8RB	NM_001557	interleukin 8 receptor, beta	1,16	0,07
CCR3	NM_001837	chemokine (C-C motif) receptor 3	1,16	0,07
IL3RA	NM_002183	interleukin 3 receptor, alpha (low affinity)	1,15	0,06
IL19	NM_013371,	interleukin 19	1,14	0,06
TNFRSF17	Z29575	tumor necrosis factor receptor superfamily, member 17	1,13	0,05
IFIH1	NM_022168	interferon induced with helicase C domain 1	1,13	0,05
IL1F5	AF186094	interleukin 1 family, member 5 (delta)	1,13	0,05
SOCS7	AI968839	suppressor of cytokine signaling 7	1,12	0,05
IRAK1BP1	AI561173	interleukin-1 receptor-associated kinase 1 binding protein 1	1,12	0,05
TNFRSF4	BC040257	tumor necrosis factor receptor superfamily, member 4	1,12	0,05
CCBP2	AI088640	chemokine binding protein 2	1,12	0,05
IFRD2	BC001327	interferon-related developmental regulator 2	1,11	0,05
CCL28	AF110384	chemokine (C-C motif) ligand 28	1,11	0,04
ISGF3G	NM_006084	interferon-stimulated transcription factor 3, gamma 48kDa	1,10	0,04
IL23R	NM_144701	interleukin 23 receptor	1,10	0,04
CCL19	U88321	chemokine (C-C motif) ligand 19	1,10	0,04
TRAF3	AI721219	TNF receptor-associated factor 3	1,09	0,04
CCL14	NM_004166	chemokine (C-C motif) ligand 14	1,09	0,04
CCL7	CD521885	chemokine (C-C motif) ligand 7	1,09	0,04
TNIP1	NM_006058	TNFAIP3 interacting protein 1	1,09	0,04
XCR1	NM_005283	chemokine (C motif) receptor 1	1,09	0,04
CXCL5	AK026546	chemokine (C-X-C motif) ligand 5	1,09	0,04
IRF2BP1	BC038222	interferon regulatory factor 2 binding protein 1	1,08	0,03
IL29	AY129150	interleukin 29 (interferon, lambda 1)	1,08	0,03
IL1R2	NM_004633	interleukin 1 receptor, type II	1,08	0,03

CXCL11	AF030514	chemokine (C-X-C motif) ligand 11	1,08	0,03
CKLF	AI825627	chemokine-like factor	1,07	0,03
CCL16	BC096352	chemokine (C-C motif) ligand 16	1,07	0,03
TRAF3	NM_003300	TNF receptor-associated factor 3	1,06	0,03
IRF8	AI073984	interferon regulatory factor 8	1,06	0,03
IL6R	NM_000565	interleukin 6 receptor	1,06	0,03
IL28B	NM_172139	interleukin 28B (interferon, lambda 3)	1,06	0,02
TRAF1	AA922208	TNF receptor-associated factor 1	1,06	0,02
IFRD2	BC028000, Y1	interferon-related developmental regulator 2	1,06	0,02
IL8RA	NM_000634	interleukin 8 receptor, alpha	1,06	0,02
IL1B	M15330	interleukin 1, beta	1,05	0,02
XCL1	U23772	chemokine (C motif) ligand 1	1,05	0,02
IL16	BC040272	interleukin 16 (lymphocyte chemoattractant factor)	1,05	0,02
CXCL16	AF275260	chemokine (C-X-C motif) ligand 16	1,05	0,02
CCL11	AI357416, NN	chemokine (C-C motif) ligand 11	1,04	0,02
IL22	BC070261	interleukin 22	1,04	0,02
IFRD1	AA747426	interferon-related developmental regulator 1	1,04	0,02
IFNK	AF146759	interferon, kappa	1,04	0,02
IFNA17	M38289	interferon, alpha 17	1,03	0,01
CX3CR1	U20350	chemokine (C-X3-C motif) receptor 1	1,03	0,01
IL7	NM_000880	interleukin 7	1,03	0,01
IL1F8	AF200494	interleukin 1 family, member 8 (eta)	1,03	0,01
IL1F9	AY359111	interleukin 1 family, member 9	1,03	0,01
IL18RAP	NM_003853	interleukin 18 receptor accessory protein	1,02	0,01
CCL13	NM_005408	chemokine (C-C motif) ligand 13	1,02	0,01
IL3	NM_000588	interleukin 3 (colony-stimulating factor, multiple)	1,02	0,01
IL12RB2	NM_001559	interleukin 12 receptor, beta 2	1,02	0,01
IL10	BC022315	interleukin 10	1,02	0,01
IL26	AJ251549	interleukin 26	1,01	0,00
CXCL9	NM_002416	chemokine (C-X-C motif) ligand 9	1,01	0,00
IL12B	NM_002187	interleukin 12B (natural killer cell stimulatory factor 2, cytotoxic lymphocyte ma	1,00	0,00
IL17F	AF332389	interleukin 17F	1,00	0,00
IL20	AY358320	interleukin 20	1,00	0,00
IL1RL1	AL117622	interleukin 1 receptor-like 1	1,00	0,00
CCL5	NM_002985	chemokine (C-C motif) ligand 5	-1,01	0,00
CCL21	NM_002989	chemokine (C-C motif) ligand 21	-1,01	0,00
CCR9	AF145439	chemokine (C-C motif) receptor 9	-1,01	0,00
TNF	NM_000594	tumor necrosis factor (TNF superfamily, member 2)	-1,01	0,00
IL1F6	DA669265	interleukin 1 family, member 6 (epsilon)	-1,01	0,00
CXCR3	NM_001504	chemokine (C-X-C motif) receptor 3	-1,01	0,00
TNFSF14	AF064090	tumor necrosis factor (ligand) superfamily, member 14	-1,01	-0,01
IL22RA1	NM_021258	interleukin 22 receptor, alpha 1	-1,01	-0,01
CCR4	BC071751	chemokine (C-C motif) receptor 4	-1,02	-0,01
TRAP1	NM_016292	TNF receptor-associated protein 1	-1,02	-0,01
CXCR6	NM_006564	chemokine (C-X-C motif) receptor 6	-1,02	-0,01
IL27RA	NM_004843	interleukin 27 receptor, alpha	-1,02	-0,01
TNFRSF7	NM_001242	tumor necrosis factor receptor superfamily, member 7	-1,03	-0,01
CCL25	CR603063	chemokine (C-C motif) ligand 25	-1,03	-0,01
IFNAR1	AA811138	interferon (alpha, beta and omega) receptor 1	-1,03	-0,01
IRF5	BF223643	interferon regulatory factor 5	-1,03	-0,01
TNFRSF9	NM_001561	tumor necrosis factor receptor superfamily, member 9	-1,04	-0,02
IRAK4	NM_016123	interleukin-1 receptor-associated kinase 4	-1,04	-0,02
IRF1	NM_002198	interferon regulatory factor 1	-1,04	-0,02
TNFRSF13B	NM_012452	tumor necrosis factor receptor superfamily, member 13B	-1,04	-0,02
ILF2	NM_004515	interleukin enhancer binding factor 2, 45kDa	-1,05	-0,02
TNFRSF17	NM_001192	tumor necrosis factor receptor superfamily, member 17	-1,06	-0,02
TNFRSF19L	AW571669	tumor necrosis factor receptor superfamily, member 19-like	-1,06	-0,02
NFKB1	M55643	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 (p105)	-1,07	-0,03
IL24	NM_006850	interleukin 24	-1,07	-0,03
IL2RB	NM_000878	interleukin 2 receptor, beta	-1,07	-0,03
IL5	BC069137	interleukin 5 (colony-stimulating factor, eosinophil)	-1,08	-0,03
IL2RA	X01057	interleukin 2 receptor, alpha	-1,08	-0,03

IL18BP	AI521549	interleukin 18 binding protein	-1,08	-0,03
CCR7	NM_001838	chemokine (C-C motif) receptor 7	-1,08	-0,03
ISG20	U88964	interferon stimulated exonuclease gene 20kDa	-1,08	-0,03
NFKBIL2	AB209126	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-like 2	-1,09	-0,04
CCL23	NM_005064	chemokine (C-C motif) ligand 23	-1,09	-0,04
IL11	NM_000641	interleukin 11	-1,09	-0,04
IRF2	NM_002199	interferon regulatory factor 2	-1,10	-0,04
ILF3	NM_004516	interleukin enhancer binding factor 3, 90kDa	-1,10	-0,04
TNIP2	AA522816	TNFAIP3 interacting protein 2	-1,11	-0,05
TNFSF8	AI936516	tumor necrosis factor (ligand) superfamily, member 8	-1,11	-0,05
CCL22	U83171	chemokine (C-C motif) ligand 22	-1,12	-0,05
IL17B	NM_014443	interleukin 17B	-1,12	-0,05
CX3CL1	U84487	chemokine (C-X3-C motif) ligand 1	-1,12	-0,05
IFNW1	NM_002177	interferon, omega 1	-1,12	-0,05
IL22RA2	NM_052962	interleukin 22 receptor, alpha 2	-1,12	-0,05
IL5RA	NM_000564	interleukin 5 receptor, alpha	-1,12	-0,05
IL10RB	BC001903	interleukin 10 receptor, beta	-1,13	-0,05
IL4	NM_000589	interleukin 4	-1,13	-0,05
IL28RA	AW340139	interleukin 28 receptor, alpha (interferon, lambda receptor)	-1,13	-0,05
IFNA2	NM_000605	interferon, alpha 2	-1,13	-0,05
IRF7	NM_004030	interferon regulatory factor 7	-1,14	-0,06
IL17RC	AI560217	interleukin 17 receptor C	-1,14	-0,06
TNFSF5IP1	NM_020232	tumor necrosis factor superfamily, member 5-induced protein 1	-1,14	-0,06
IFNA7	NM_021057	interferon, alpha 7	-1,14	-0,06
TNFRSF8	NM_001243	tumor necrosis factor receptor superfamily, member 8	-1,14	-0,06
IL2RG	NM_000206	interleukin 2 receptor, gamma (severe combined immunodeficiency)	-1,15	-0,06
IFNA16	NM_002173	interferon, alpha 16	-1,15	-0,06
TNFSF11	AF053712	tumor necrosis factor (ligand) superfamily, member 11	-1,15	-0,06
IL23A	NM_016584	interleukin 23, alpha subunit p19	-1,15	-0,06
IRAK2	NM_001570	interleukin-1 receptor-associated kinase 2	-1,16	-0,06
IL13RA1	NM_001560	interleukin 13 receptor, alpha 1	-1,16	-0,06
TRAF7	AL136921	TNF receptor-associated factor 7	-1,16	-0,06
IFNA6	BC069471	interferon, alpha 6	-1,16	-0,07
IL17C	NM_013278	interleukin 17C	-1,16	-0,07
IL1RAPL1	NM_014271	interleukin 1 receptor accessory protein-like 1	-1,17	-0,07
CMKOR1	BE552368	chemokine orphan receptor 1	-1,17	-0,07
IRF2BP2	BF968057	interferon regulatory factor 2 binding protein 2	-1,19	-0,07
IL2	NM_000586	interleukin 2	-1,19	-0,08
IFNGR1	AI458949	interferon gamma receptor 1	-1,19	-0,08
IL10RA	NM_001558	interleukin 10 receptor, alpha	-1,20	-0,08
CCL1	DA620119	chemokine (C-C motif) ligand 1	-1,20	-0,08
IFNGR1	AK127636, AF	interferon gamma receptor 1	-1,25	-0,10
TNFAIP8L2	AF271774	tumor necrosis factor, alpha-induced protein 8-like 2	-1,25	-0,10
SOCS6	NM_004232	suppressor of cytokine signaling 6	-1,26	-0,10
CMKLR1	U79526	chemokine-like receptor 1	-1,26	-0,10
IL17A	U32659	interleukin 17A	-1,26	-0,10
IFNGR1	NM_000416	interferon gamma receptor 1	-1,27	-0,10
IFNAR2	AI653318	interferon (alpha, beta and omega) receptor 2	-1,27	-0,11
IL18R1	NM_003855	interleukin 18 receptor 1	-1,28	-0,11
CCRL2	AF015524	chemokine (C-C motif) receptor-like 2	-1,29	-0,11
IFNGR2	NM_005534	interferon gamma receptor 2 (interferon gamma transducer 1)	-1,30	-0,11
CXCL13	NM_006419	chemokine (C-X-C motif) ligand 13 (B-cell chemoattractant)	-1,30	-0,11
IL1R1	NM_000877	interleukin 1 receptor, type I	-1,35	-0,13
CCR2	NM_000647	chemokine (C-C motif) receptor 2	-1,39	-0,14
CCR6	NM_004367	chemokine (C-C motif) receptor 6	-1,39	-0,14
IRF4	NM_002460	interferon regulatory factor 4	-1,40	-0,15
IL17RD	BC038369	interleukin 17 receptor D	-1,41	-0,15
TRAF5	NM_004619	TNF receptor-associated factor 5	-1,43	-0,16
TNFAIP2	NM_006291	tumor necrosis factor, alpha-induced protein 2	-1,49	-0,17
CCL24	BP338501	chemokine (C-C motif) ligand 24	-1,52	-0,18
IRF2BP2	BG485163	interferon regulatory factor 2 binding protein 2	-1,53	-0,18
CCR1	AI421071	chemokine (C-C motif) receptor 1	-1,55	-0,19

TNFSF10	NM_003810	tumor necrosis factor (ligand) superfamily, member 10	-1,59	-0,20
TNFRSF1B	NM_001066	tumor necrosis factor receptor superfamily, member 1B	-1,59	-0,20
IL7R	NM_002185	interleukin 7 receptor	-1,61	-0,21
TNFRSF1A	NM_001065	tumor necrosis factor receptor superfamily, member 1A	-1,63	-0,21
IFI16	NM_005531	interferon, gamma-inducible protein 16	-1,65	-0,22
CKLF	BG533580	chemokine-like factor	-1,72	-0,24
IFITM3	BF338947	interferon induced transmembrane protein 3 (1-8U)	-1,80	-0,26
TNFSF4	NM_003326	tumor necrosis factor (ligand) superfamily, member 4 (tax-transcriptionally activ	-1,83	-0,26
IRF3	NM_001571	interferon regulatory factor 3	-1,83	-0,26
SOCS3	AI244908	suppressor of cytokine signaling 3	-1,99	-0,30
ISG20L2	NM_030980	interferon stimulated exonuclease gene 20kDa-like 2	-2,05	-0,31
IL20RA	NM_014432,	interleukin 20 receptor, alpha	-2,08	-0,32
IRAK1BP1	BG545769	interleukin-1 receptor-associated kinase 1 binding protein 1	-2,49	-0,40
IFITM2	NM_006435	interferon induced transmembrane protein 2 (1-8D)	-2,83	-0,45
CMKOR1	AI817041	chemokine orphan receptor 1	-2,96	-0,47
IL15RA	NM_002189	interleukin 15 receptor, alpha	-3,14	-0,50
IFITM1	AA749101	interferon induced transmembrane protein 1 (9-27)	-3,19	-0,50
TNFRSF11B	BF433902	tumor necrosis factor receptor superfamily, member 11b (osteoprotegerin)	-3,31	-0,52
IL11RA	NM_004512	interleukin 11 receptor, alpha	-4,28	-0,63
TNFRSF19	BF432648	tumor necrosis factor receptor superfamily, member 19	-5,67	-0,75
CXCL14	NM_004887	chemokine (C-X-C motif) ligand 14	-8,12	-0,91
IL17D	BE856748	interleukin 17D	-15,04	-1,18
CXCL12	NM_000609	chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1)	-43,38	-1,64