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p38 MAPK inhibitors suppress biomarkers of hypertension end-organ damage, osteopontin and plasminogen activator inhibitor-1

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Abstract

The assessment of target organ damage is important in defining the optimal treatment of hypertension and blood pressure-related cardiovascular disease. The aims of the present study were (1) to investigate candidate biomarkers of target organ damage, osteopontin (OPN) and plasminogen activator inhibitor-1 (PAI-1), in models of malignant hypertension with well characterized end-organ pathology; and (2) to evaluate the effects of chronic treatment with a p38 MAPK inhibitor. Gene expression, plasma concentrations, and renal immunohistochemical localization of OPN and PAI-1 were measured in stroke-prone spontaneously hypertensive rats on a salt–fat diet (SFD SHR-SP) and in spontaneously hypertensive rats receiving N^{ω}-nitro-L-arginine methyl ester (L-NAME SHR). Plasma concentrations of OPN and PAI-1 increased significantly in SFD SHR-SP and L-NAME SHR as compared with controls, (2.5–4.5-fold for OPN and 2.0–9.0-fold for PAI-1). The plasma levels of OPN and PAI-1 were significantly correlated with the urinary excretion of albumin ($p < 0.0001$). Elevations in urinary albumin, plasma OPN and PAI-1 were abolished by chronic treatment (4–8 weeks) with a specific p38 MAPK inhibitor, SB-239063AN. OPN immunoreactivity was localized predominantly in the apical portion of tubule epithelium, while PAI-1 immunoreactivity was robust in glomeruli, tubules and renal artery endothelium. Treatment with the p38 MAPK inhibitor significantly reduced OPN and PAI-1 protein expression in target organs. Kidney gene expression was increased for OPN (4.9- and 7.9-fold) and PAI-1 (2.8- and 11.5-fold) in SFD SHR-SP and L-NAME SHR, respectively. *In-silico* pathway analysis revealed that activation of p38 MAPK was linked to OPN and PAI-1 via SP1, c-fos and c-jun; suggesting that these pathways may play an important role in p38 MAPK-dependent hypertensive renal dysfunction. The results suggest that enhanced OPN and PAI-1 expression reflects end-organ damage in hypertension and that suppression correlates with end-organ protection regardless of overt antihypertensive action.

Keywords: *Osteopontin, plasminogen activator inhibitor-1, hypertension, biomarkers*

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Introduction

Hypertension target organ damage (HTN-TOD) is associated with tissue injury and remodelling in kidney, heart, blood vessels, brain, and retina. Evidence suggests that a wide variety of interrelated biological processes, i.e. oxidative stress, inflammation, thrombosis, matrix reorganization and apoptosis, contribute to the tissue damage (Luft et al. 1999). HTN-TOD is usually insidious, progressing slowly without clinical manifestations, and simple biomarkers for early detection are limited and not routinely employed for the management of HTN. Recent clinical results, however, suggest that biomarkers of HTN-TOD may help guide therapy. In particular, elevated urinary albumin excretion in HTN patients is directly related to left ventricular hypertrophy (LVH) and cardiovascular events, but is independent of BP and other common cardiovascular risk factors (Wachtell et al. 2003, Olsen et al. 2004, Ibsen et al. 2005). Thus, antihypertensive therapy is not optimal if it does not adequately address target organ damage and it is suggested that more aggressive treatment should be considered for refractory patients (Ibsen et al. 2005).

Osteopontin (OPN), a multifunctional cytokine, and plasminogen activator inhibitor-1 (PAI-1), a SERPIN regulator of haemostasis, have been implicated as contributing risk factors and plasma biomarkers for cardiovascular disease in diabetes and hypertension (Kaikita et al. 2001, Srikumar et al. 2002, Gauer et al. 2003, Juhan-Vague et al. 2003, Horrevoets 2004, Junaid & Amara 2004). Both of these secreted proteins are associated with tissue injury/remodelling and are the most highly expressed genes in rat aortic smooth muscles cells stimulated with angiotensin-II (Campos et al. 2003). *In vitro*, the up-regulation of OPN and PAI-1 by angiotensin-II involves activation of mitogen-activated protein kinase (MAPK) signalling pathways and is abolished by selective inhibitors of ERK and p38 MAPK signal transduction (Lee et al. 1999, Chen et al. 2000, Campos et al. 2003, Brown et al. 2004). Previous *in vivo* studies in our laboratory have demonstrated that activation of p38 MAPK plays an important role in endothelial dysfunction and target organ damage in malignant hypertension (Behr et al. 2001, Ju et al. 2003, Lenhard et al. 2003, Olzinski et al. 2005). These studies demonstrate that chronic treatment with selective p38 MAPK inhibitors dramatically reduced hypertensive target organ damage in the brain, heart, kidney and vasculature without direct haemodynamic effects.

The aims of the present *in vivo* study were to examine OPN and PAI-1 as biomarkers of target organ damage in models of malignant hypertension with well-defined end-organ pathology and to evaluate the effects of target organ protection induced by chronic treatment with a selective p38 inhibitor, SB-239063AN p38 MAPK ($IC_{50} = 46$ nM, 4- and 600-fold selectivity versus JNK and ERK, respectively). The results suggest that plasma levels of OPN and PAI-1 reflect target organ damage, represent distinct end-organ changes and allow evaluation of target organ protection with p38 MAPK inhibitor treatment. Microarray analysis of the hypertensive kidney suggests several p38 MAPK-dependent pathways regulating PAI-1 and OPN expression.

Materials and methods

Animal models

Spontaneously hypertensive stroke-prone (SHR-SP) rats. Male SHR-SP rats were obtained from Charles River (Raleigh, NC, USA). At 11 weeks of age, the SHR-SP

rats were randomized into three groups, and fed either powdered chow diet (Purina 5001) with water *ad libitum* (SHR-SP group, $n=13$); a high-salt/high-fat diet (SFD group, $n=34$) consisting of 1% NaCl in the drinking water, and 24.5% fat in the chow (from Harlan TekLad, Madison, WI, USA) or SFD with a highly selective p38 MAPK inhibitor SB-239063AN (Ju et al. 2003), added to the diet (1200 ppm), (SFD + SB-239063AN group, $n=31$) for the duration of the study (8 weeks).

L-NAME SHR. Male spontaneously hypertensive rats (SHR, $n=26$, Taconic Farms) were included in the study at 10 weeks of age. All animals initially received powdered chow diet (Purina 5001) and water *ad libitum*. Rats were then randomized into three groups; SHR ($n=8$), L-NAME (N^{ω}-nitro-L-arginine methyl ester, 185 mmol l^{-1} in drinking water, $n=10$) and L-NAME + SB-239063AN ($n=8$). Three days before the addition of L-NAME to the drinking water, SB-239063AN (1200 ppm) was added to the powdered chow of the treatment group and both were continued for the duration of the study (4 weeks). Due to a more rapid onset of morbidity/mortality as compared with the SFD SHR-SP, the study was terminated at 4 weeks.

All rats were placed in metabolism cages for 48 h at baseline and weekly thereafter for urine collection and the determination of food and water consumption. Blood samples were collected into ethylenediamine tetra-acetic acid (EDTA) from the tail vein or inferior vena cava, and plasma was prepared immediately. As described previously, moribund animals were promptly euthanized (Behr et al. 2001). Experiments were conducted in accord with the *Guide for Care and Use of Laboratory Animals* (1996) and experimental protocols were reviewed and approved by the GlaxoSmithKline Animal Care and Use Committee.

Urinary excretion of albumin

Albuminuria was determined using an immunoturbidometric assay optimized for the determination of rat albumin in an Olympus AU640 AutoAnalyzer (KRA-010/020 Kamiya Biomedical Co., Seattle, WA, USA). Albumin excretion was calculated by multiplying the 24-h urine volume by the urinary albumin concentration.

Plasma OPN and PAI-1

OPN and PAI-1 concentrations were determined in EDTA plasma using OPN Ag ELISA (Assay Designs, Ann Arbor, MI, USA) and rat PAI-1 Ag ELISA (HYPHEN BioMed, Neuville-Sur-Oise France). Assays were performed according to the manufacturer's instructions.

OPN and PAI-1 immunohistochemistry

Animals were anaesthetized with 5% isoflurane. Kidneys were rapidly removed, weighed, fixed in 10% neutral buffered formalin for 24 h, transferred to 70% ethanol, and processed for paraffin embedding. Paraffin thin sections were deparaffinized, rehydrated and subjected to heat-induced epitope retrieval (HIER) before staining on DAKO Autostainer®. Briefly, sections were blocked with 3% hydrogen peroxide followed by a protein block (DakoCytomation, Carpenteria, CA, USA). Sections were stained with either a mouse anti-human OPN (University of Iowa Hybridoma Bank) at a dilution of 1:50 or a rabbit anti-rat PAI-1 (American Diagnostica, Inc., Stamford,

CT, USA) at a concentration of 10 μg ml^{-1}. Specific staining was assessed by examining standard control slides, i.e. deletion of the primary antibody step and substitution of primary antibody with species and concentration matched isotype control immunoglobulins. Slides were incubated with either mouse or rabbit Envision® labelling polymer system (DakoCytomation). Staining was detected with 3,3-diaminobenzidine (DAB) and counterstained with haematoxylin. Slides were dehydrated, cleared and coverslipped.

All slides were scored, blinded to treatment, on 2 separate days by a certified histopathologist (K. F.) with the following scoring system: 0 = negative or very minimal; 1 = minimal or slight; 2 = mild; 3 = moderate; and 4 = marked staining.

Transcriptomic microarray analysis

Frozen whole kidney samples (8 week SHR-SP, SFD SHR-SP and 4 week SHR, L-NAME SHR, $n = 6$ per group) were pulverized on dry ice and processed individually. Approximately 100 mg of tissue were further homogenized using a Mixer Mill with Trizol reagent (Invitrogen Corp., Carlsbad, CA, USA) and the resulting lysate was purified using the RNeasy Mini Kit (Qiagen, Inc., Valencia, CA, USA) according to the manufacturer's instructions. Double-stranded cDNA was synthesized from total RNA via oligo-T7-mediated reverse transcription. Biotin-labelled cRNA was synthesized using an *in vitro* transcription (IVT) reaction with the Enzo BioArray High Yield RNA transcript labelling Kit (Enzo Diagnostics, Inc., Farmingdale, NY, USA). Samples were purified and quality controlled according to the manufacturer's recommendations. Standard Affymetrix protocols were used to fragment cRNA, which was hybridized to a RG230A genechip for 16–18 h at 45°C. An Affymetrix Genechip Fluidics Station 450 was used to perform standard washing and streptavidin/phycoerythrin staining. The chips were scanned using an Affymetrix Genechip scanner 3000.

Affymetrix Genechip version 5.0 software was used for raw data processing. CEL files were loaded into Rosetta Resolver (version 4.0, Kirkland, MA, USA), samples were normalized and processed according to the Resolver error model for Affymetrix high-density oligo expression arrays. The ratio builder and analysis of variance (ANOVA) tools were used to generate gene expression-fold changes and significance values. The Benjamini and Hochberg method was used to apply a false discovery rate correction set at a 0.1 false discovery rate threshold. Ratios were built between SFD SHR-SP and L-NAME SHR and their respective controls for equivalent time points. Alterations in expression are presented for the genes changing $\geq$2-fold, $\leq$-2-fold and $p < 0.01$.

In-silico *pathway analysis*

Pathway analysis was performed using a database of interacting proteins assembled via manual curation of the literature. This database includes protein–protein interactions, protein–DNA interactions, enzyme–substrate interactions, etc. These pairwise interactions were assembled into a network of interacting proteins. The network was filtered to eliminate gene pairs in which either gene was not expressed in the kidney (according to the GeneLogic database of mRNA expression). Every gene in this network was tested to determine whether its network neighbourhood overlapped significantly with the dysregulated genes in either disease model. Significance was determined via Fisher's exact test of proportions followed by Bonferroni correction. Genes whose network neighbourhoods overlap significantly with the dysregulated

gene lists are considered likely to play a role in the dysregulation observed in the disease model. The two lists of genes that interact significantly with the two dysregulated gene lists were then intersected to determine the subset that interact significantly with both dysregulated gene lists. Finally, another network analysis was performed to identify a further subset that interact significantly with both dysregulated lists, and are phosphorylated by p38 MAPK (MAPK14), and transcriptionally regulate either, or both, OPN and PAI-1.

Statistical analysis

All summary values are expressed as the mean ± standard error of the mean (SEM). Multiple comparisons of the means were made by analysis of variance followed by post-hoc analysis with the Bonferroni correction for multiple comparisons. All statistical analyses were performed using InStat (GraphPad Software, Inc., San Diego, CA, USA) and $p \leq 0.05$ was considered as being statistically significant.

Results

Time course of albuminuria

Urinary albumin excretion was determined from urine samples collected over 24 hr in SHR-SP and SHR animals. The addition of SFD to the SHR-SP resulted in a progressive increase in albuminuria with significant elevations observed at 5.5 weeks as compared with baseline (Figure 1a). No significant changes in urinary albumin excretion were noted in the SHR-SP control group. Comparatively, the L-NAME SHR is a more aggressive model of hypertension, and an accelerated pattern of albuminuria was observed in SHRs receiving L-NAME during the 4-week study (data not shown).

Plasma OPN and PAI-1

OPN and PAI-1 concentrations were measured in plasma samples from both animal models throughout the course of the study. Both OPN and PAI-1 concentrations correlated with urinary albumin excretion in the SHR-SP model (Figure 1b, $r^2 = 0.72$; $p < 0.0001$; Figure 1c, $r^2 = 0.78$; $p < 0.0001$; OPN and PAI-1, respectively) and followed a time course comparable with the albuminuria. A similar relationship to albumin excretion was observed in the L-NAME model, albuminuria versus PAI-1, $r^2 = 0.52$; $p < 0.05$ (data not shown).

Effect of p38 MAPK inhibitor (SB-239063AN)

The effect of treatment with a selective p38 MAPK inhibitor on plasma OPN and PAI-1 concentrations and albumin excretion was examined in SFD SHR-SP (for 8 weeks) and L-NAME SHR (for 4 weeks) models.

The introduction of the SFD to SHR-SP and L-NAME to the SHR progressively increased plasma concentrations of both OPN and PAI-1 at all time points examined. In comparison, OPN and PAI-1 plasma concentrations were reduced in groups treated chronically with a selective p38 inhibitor, SB-239063AN (Figure 2, b, c, e, and f). Similarly, urinary albumin excretion was attenuated by treatment with the p38 inhibitor (Figure 2, a and d).

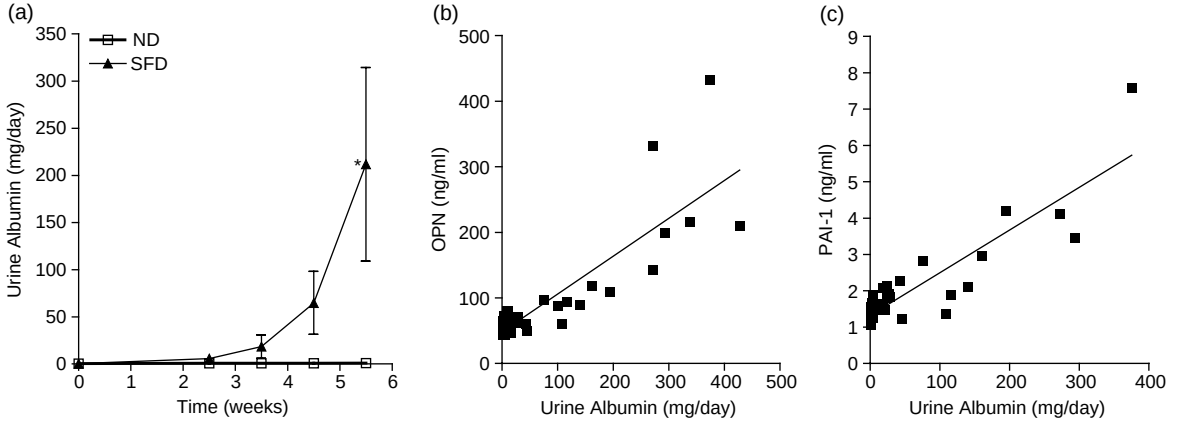

Figure 1. Time-dependent increase in urinary albumin excretion and its correlation to plasma OPN and PAI-1. The introduction of SFD induced a progressive increase in urinary albumin excretion (a) in the SHR-SP (211 ± 102 versus 0.35 ± 0.03, 5.5 versus 0 weeks, respectively, $^{\star}p < 0.05$). Values are mean $\pm$ SEM. At the 4-week interval, urinary albumin excretion was correlated with plasma levels of OPN ($r^2 = 0.72$; $p < 0.0001$, $n = 37$) and PAI-1 ($r^2 = 0.78$; $p < 0.0001$, $n = 32$) (b and c, respectively).

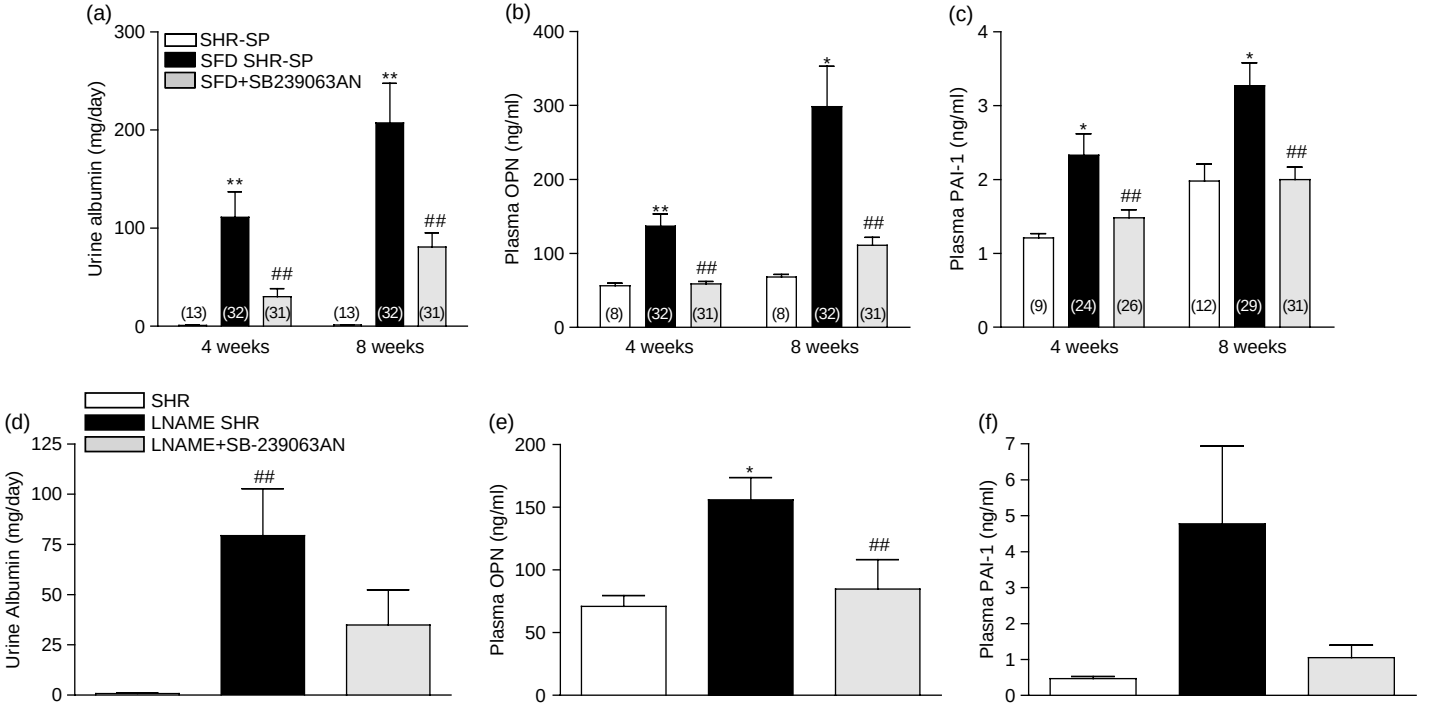

Figure 2. Effect of chronic treatment with SB-239063AN on urine albumin excretion and plasma concentrations of OPN and PAI-1 in models of malignant hypertension. The significant increases in albumin excretion (a), plasma OPN (b) and plasma PAI-1 (c) in the SFD group were all reduced by treatment with SB-239063AN. Treatment results showed similar trends in the L-NAME groups at 4 weeks (d–f). $^{*}p < 0.05$, $^{**}p < 0.01$ SHR-SP versus SFD and SHR versus L-NAME; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ SFD versus SFD+SB-239063AN, and L-NAME versus L-NAME+SB-239063AN. All values are mean±SEM.

OPN and PAI-1 immunohistochemistry

The immunohistochemical localization of OPN and PAI-1 was examined in thin sections of kidney from both models. Immunoreactive OPN was minimal in kidney sections from control SHR-SP and SHR groups (Figure 3a). In the SFD SHR-SP and the L-NAME SHR groups, OPN immunoreactivity was localized to the tubules of the inner strip of the outer medulla (Figure 3b), mostly in the pars recta (S3 segment and descending loop). Specifically, OPN immunoreactivity was located in the apical portion of epithelial cells, and was more cytoplasmic than nuclear. In the tip of the papillae, the pelvic urothelium stained positive but no staining was seen in the transitional epithelium (data not shown). OPN immunoreactivity in the kidney was

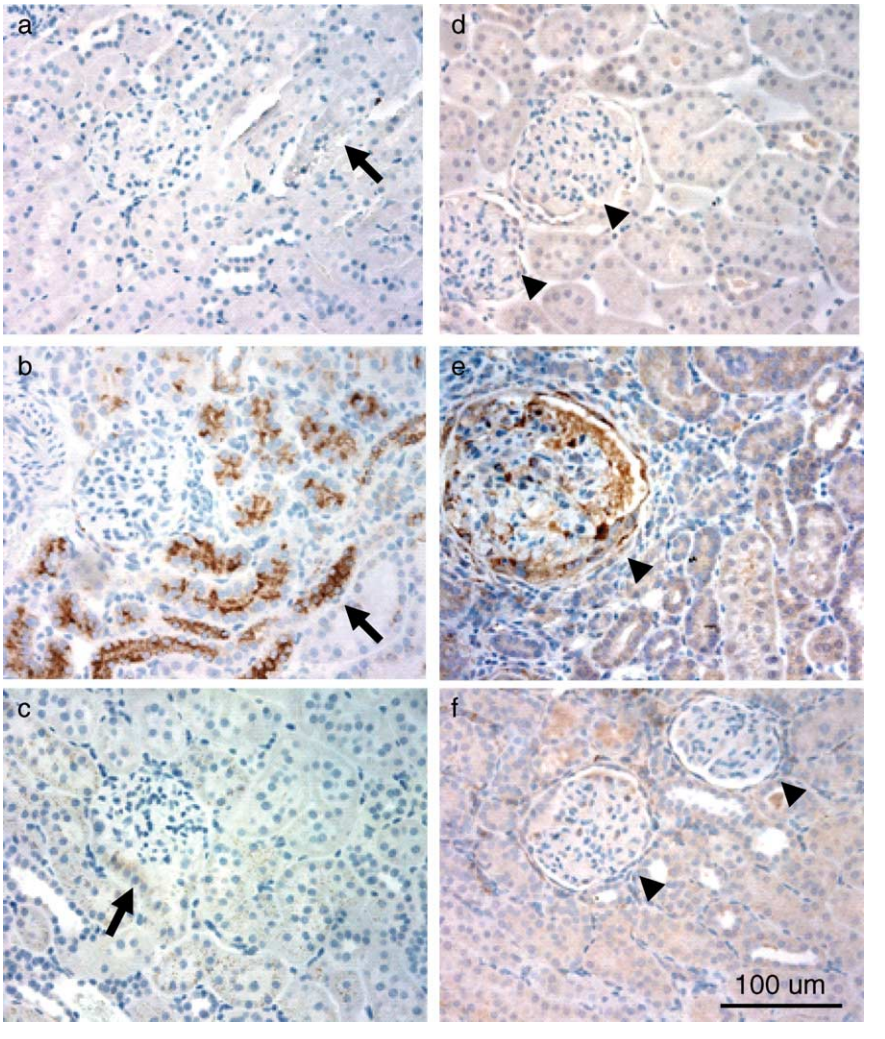

Figure 3. Immunohistochemical localization of OPN and PAI-1 in the kidney. Minimal OPN and PAI-1 staining was observed in control SHR-SP kidney (a and d, respectively). The addition of a salt–fat diet in the SHR-SP increased tubular (see arrow) expression of OPN (b). PAI-1 expression (e) was also increased primarily in the glomeruli (see arrowhead) and to a lesser extent in tubules. OPN and PAI-1 expression in the kidney was attenuated by chronic treatment with SB-239063AN (c and f, respectively).

significantly reduced in groups receiving SB-239063AN (Figure 3c). The immunohistochemical score, specifically for the tubules (Figure 4a), increased with SFD and decreased with inhibitor treatment (1 ± 0, 3.8 ± 0.1 and 2.5 ± 0.25 for the SHR-SP, SFD and SFD + SB-239063AN, respectively). Similar results were obtained in the L-NAME model (data not shown).

PAI-1 histochemical immunoreactivity was negligible in the control SHR-SP and SHR kidney (Figure 3d). In contrast, PAI-1 immunoreactivity was localized mainly to sclerotic glomeruli in SFD SHR-SP and L-NAME SHR groups and to a lesser extent in the proximal tubules (Figure 3e). Within the glomeruli, PAI-1 was most prominent in the endothelial cells, mesangial cells and podocytes. Chronic treatment with the p38 inhibitor, SB-239063AN, significantly attenuated the positively stained area in the kidney (Figure 3f). Immunohistochemical scoring for glomeruli (Figure 4b) was 0.6 ± 0.3, 3.0 ± 0.1 and 1.9 ± 0.5 for the SHR control, L-NAME-SHR and L-NAME + SB-239063AN groups, respectively. Results were similar for the SFD SHR-SP model (data not shown).

Kidney microarray and pathway analysis in malignant hypertension

Kidney microarray analysis was performed in order to place OPN and PAI-1 renal expression in the context of genes regulated in malignant hypertension. In SFD SHR-SP, 187 genes were increased and eight genes were decreased when compared with the SHR-SP receiving a normal diet. OPN was increased 4.9-fold and PAI-1 was increased 2.8-fold in this group (see Appendix 1 for all genes changing in the SFD SHR-SP). In the L-NAME SHR compared with SHR, there were 413 genes that were increased and 263 were decreased. OPN was increased 7.9-fold and PAI-1 was increased 11.5-fold (see Appendix 2 for all genes changing in the L-NAME SHR).

In-silico analysis of the dysregulated gene lists identified a list of 24 genes that significantly interact with the sets of dysregulated genes in both disease models. Further network analysis revealed that three of these are transcription factors that can be phosphorylated by p38 MAPK and transcriptionally regulate OPN and PAI-1

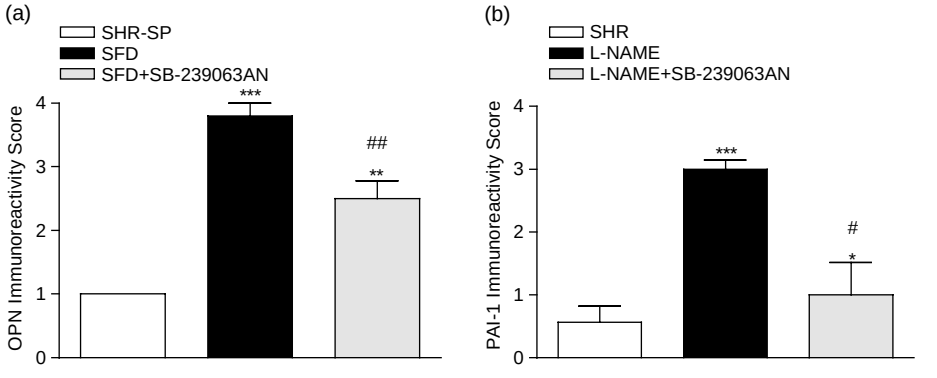

Figure 4. Immunohistochemical scoring of OPN and PAI-1 immunoreactivity in the kidneys. The addition of L-NAME increased OPN and PAI-1 immunohistochemical staining in the SHR kidney (a and b, respectively). The increase in OPN and PAI-1 staining was attenuated by treatment with SB-239063AN. Values are mean $\pm$ SEM. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ SHR versus L-NAME, and SHR-SP versus SFD; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ L-NAME versus L-NAME + SB-239063AN and SFD versus SFD + SB-239063AN.

(Figure 5). Activation of p38 MAPK was linked to OPN and PAI-1 via SP1, c-fos and c-jun. The results suggest that these pathways may play an important role in p38 MAPK-dependent hypertensive renal dysfunction.

Discussion

In the present study, plasma concentrations and expression patterns of OPN and PAI-1 were examined in models of malignant hypertension. The primary findings were: (1) OPN and PAI-1 *in-situ* immunoreactivity and plasma concentrations increased progressively in hypertension, (2) plasma levels of both proteins correlated with urinary albumin excretion, reflecting progressive renal damage, (3) OPN and PAI-1 had differential localization patterns in the kidney, (4) chronic treatment with a selective p38 MAPK inhibitor reduced tissue and plasma levels of OPN and PAI-1 concordant with target organ protection, and (5) microarray and pathway analysis identified putative mechanisms of hypertension target organ damage. The results suggest that plasma levels of OPN and PAI-1 are biomarkers of target organ damage in hypertension that reflect distinct p38 MAPK-dependent remodelling events and may have utility in the assessment of novel approaches to the treatment of hypertensive disease.

OPN expression was minimal in kidneys from normotensive and moderately hypertensive animals, however, the increased expression observed in malignant hypertension is consistent with its proposed role in tissue injury/remodelling (Mazzali et al. 2002). Enhanced renal OPN immunoreactivity was localized in proximal segments of the tubule, specifically in the apical portion of the epithelium, and is very reminiscent of KIM-1 expression following renal injury (Han et al. 2002). These results are similar to the tubular expression patterns of OPN observed in rats following chronic angiotensin-II infusion (Deblois et al. 1996) and in kidney biopsies from patients with decompensated nephrosclerosis associated with essential hypertension (Thomas et al. 1998). Tubular expression of OPN is thought to play a chemotactic and/or adhesive role — recruiting macrophage and fibroblasts responsible for inflammation and matrix remodelling of the tubulointerstitium. It has been suggested that tubulointerstitial damage and fibrosis contribute importantly in the transition to salt-sensitive hypertension (Johnson et al. 2005). Consistent with this hypothesis, chronic treatment with a p38 MAPK inhibitor reduced the renal expression of OPN and attenuated interstitial fibrosis as well as salt-sensitive hypertension (Ju et al. 2003, Lenhard et al. 2003).

Like OPN, PAI-1 expression was increased in the SFD SHR-SP and L-NAME SHR models of malignant hypertension. However, the immunohistochemical localization of PAI-1 in the kidney was distinct compared with OPN. Enhanced PAI-1 immunoreactivity was localized primarily in glomeruli and to a lesser extent in proximal tubules, renal vascular endothelium and media. The results are consistent

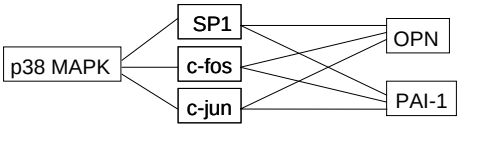

Figure 5. *In-silico* pathway analysis of microarray gene expression revealed putative p38 MAPK-dependent mechanisms of OPN and PAI-1 regulation in the hypertensive kidney. Activation of p38 MAPK was linked to PAI-1 and OPN via SP1, c-fos and c-jun. SP1, specificity protein-1; c-fos, FBJ osteosarcoma oncogene; c-jun, transforming oncogene of the avian sarcoma virus 17.

with previous observations of elevated PAI-1 gene expression in double transgenic rats (over-expression of human angiotensinogen and renin) with renal end-organ damage (Luft et al. 1999, Mervaala et al. 1999, Theuer et al. 2002). These investigators demonstrated that PAI-1 was associated with the infiltration of inflammatory cells in the kidney. As a primary inhibitor of fribinolysis, PAI-1 may play an important role in the hallmark fibrinoid arteriosclerosis observed in hypertensive renal arterioles. Chronic treatment with a p38 MAPK inhibitor preserved renal function and significantly reduced tissue PAI-1 levels in the models of malignant hypertension.

Plasma concentrations of both OPN and PAI-1 were elevated progressively in the models of malignant hypertension and were highly correlated with urinary albumin excretion. Despite a similar correlation, OPN and PAI-1 are known to have very different biological activities and exhibit distinct renal expression patterns *in situ* (above). Thus, the correlation of plasma OPN and PAI-1 with albuminuria may suggest two independent cellular processes known to regulate albumin excretion in the nephron — changes in tubular reabsorption and glomerular albumin filtration, respectively (Mathieson 2004). The origin(s) of elevated plasma OPN and PAI-1 in malignant hypertension remains to be determined.

Chronic treatment with a selective inhibitor of p38 MAPK significantly reduced plasma and tissue levels of OPN and PAI-1, and the urinary excretion of albumin. Changes in these biomarkers were associated with structural and functional improvement in kidneys. The present results extend previous reports that demonstrate efficacious end-organ protection following treatment with structurally related and diverse (unpublished) p38 MAPK inhibitors (Behr et al. 2001, 2003, Ju et al. 2003, Lenhard et al. 2003, Olzinski et al. 2005). The mechanism by which p38 inhibitors attenuate OPN and PAI-1 plasma levels is unclear, however, it is unlikely to be a primary haemodynamic action since p38 MAPK inhibitors are devoid of traditional antihypertensive activity. However, chronic haemodynamic improvements secondary to renovascular protection cannot be ruled out. In previous studies we have shown that p38 inhibitors prevent the progression of hypertension in the SFD SHR-SP (Behr et al. 2001, Ju et al. 2003) and L-NAME SHR (Olzinski et al. 2005), however endothelial function is only improved in the SHR-SP model. Evidence suggests that treatment with p38 MAPK inhibitors restore NO/ROS balance in the vessel wall by inhibiting hypertension induced up-regulation of β-nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (data not shown).

Pathway analysis based on the microarray results suggested mechanisms by which p38 MAPK may regulate OPN and PAI-1 in malignant hypertension. The three transcription factors identified (SP1, c-fos and c-jun) are activated by p38 MAPK in different *in vitro* or *in vivo* models (Fisher et al. 1998, Ma et al. 2001, Tanos et al. 2005). Furthermore, each of these transcription factors has been shown to regulate both OPN (Wang et al. 2000, Bidder et al. 2002) and PAI-1 (Datta et al. 2000, Kasza et al. 2002, Vulin & Stanley 2004) expression by interacting with respective promoter recognition sequences. This *in-silico* analysis provides a conceptual framework for further investigation into mechanisms of hypertensive target organ damage.

Progressive increases in plasma concentrations of OPN and PAI-1 were correlated with albuminuria in models of malignant hypertension and their differential renal localization suggest distinct roles in target organ damage. Conversely, plasma levels and renal expression of OPN and PAI-1 were reduced along with target organ damage in groups treated with a selective p38 MAPK inhibitor. Thus, plasma OPN and PAI-1

appear to be biomarker of p38 MAPK-dependent hypertensive target organ damage. Future biomarkers strategies may help guide aggressive treatment of hypertensive patients, especially when effective treatment modalities have only modest or indirect effects on blood pressure.

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Appendix 1

SHR-SF SFD Microarray Gene Expression Fold Changes

AFFY Probe	Gene Name	Upregulated Fold Change
1387965_at	kidney injury molecule 1	12.1
1387011_at	lipocalin 2	10.8
1374345_at	ESTs	10.4
1371406_at	polymerase I and transcript release factor (predicted)	8.6
1388547_at	claudin 4 (predicted)	7.6
1373401_at	tenascin C	6.7
1389409_at	similar to Testis derived transcript	6.7
1370080_at	heme oxygenase (decycling) 1	6.5
1370992_a_at	fibrinogen, alpha polypeptide	6.4
1368026_at	hepatoma-derived growth factor, related protein 2	6.2
1387033_at	uncoupling protein 1	6.2
1367734_at	Aldehyde reductase 1 (low Km aldose reductase) (5.8 kb PstI fragment, probably the functional gene)	6.0
1373421_at	TG interacting factor (predicted)	5.4
1369268_at	activating transcription factor 3	5.3
1370511_at	fibrinogen, B beta polypeptide	5.3
1368187_at	glycoprotein (transmembrane) nmb	5.1
1368168_at	solute carrier family 34 (sodium phosphate), member 2	5.1
1367581_a_at	secreted phosphoprotein 1 (OPN)	4.9
1368224_at	Serine protease inhibitor	4.8
1388460_at	capping protein (actin filament), gelsolin-like (predicted)	4.6
1370912_at	R.norvegicus hsp70.2 mRNA for heat shock protein 70.	4.6
1376845_at	putative ISG12(b) protein	4.5
1367712_at	tissue inhibitor of metalloproteinase 1	4.3
1368464_at	macrophage galactose N-acetyl-galactosamine specific lectin 1	4.2
1374594_at	ESTs	4.1
1367846_at	S100 calcium-binding protein A4	4.1
1387550_a_at	solute carrier family 14 (urea transporter), member 2	4.1
1368471_at	guanylate cyclase activator 2A	4.0
1367739_at	Cytochrom c oxidase subunit VIII-H (heart/muscle)	4.0
1374070_at	glutathione peroxidase 2	4.0
1368052_at	transmembrane 4 superfamily member 3	4.0
1386912_at	procollagen C-proteinase enhancer protein	3.8
1370892_at	complement component 4a	3.8
1374806_at	similar to 14-3-3 protein sigma	3.6
1370894_at	claudin 7	3.6
1375132_at	similar to Ars component B (predicted)	3.5
1390515_at	ESTs	3.5
1387202_at	intercellular adhesion molecule 1	3.4
1372691_at	uridine phosphorylase 1 (predicted)	3.4
1367998_at	secretory leukocyte peptidase inhibitor	3.4
1368921_a_at	CD44 antigen	3.4
1398421_at	nuclear factor of activated T-cells 5 (predicted)	3.4
1373908_at	ESTs	3.4
1373780_at	tetraspan 1	3.4
1389067_at	solute carrier organic anion transporter family, member 4a1	3.4
1372256_at	ESTs	3.4
1368023_at	quiescin Q6	3.4
1368259_at	prostaglandin-endoperoxide synthase 1	3.3
1389500_at	ESTs	3.3
1388902_at	ESTs	3.3
1371817_at	similar to myo-inositol 1-phosphate synthase A1	3.2
1386890_at	S100 calcium binding protein A10 (calpactin)	3.2
1386879_at	lectin, galactose binding, soluble 3	3.2
1368418_a_at	ceruloplasmin	3.1
1372219_at	similar to tropomyosin 1, embryonic fibroblast - rat	3.1
1388116_at	collagen, type 1, alpha 1	3.1
1387017_at	squalene epoxidase	3.1
1387050_s_at	kininogen 1	3.1
1367847_at	nuclear protein 1	3.1
1367749_at	lumican	3.1
1368940_at	purinergic receptor P2Y, G-protein coupled 2	3.0
1389179_at	cell death-inducing DNA fragmentation factor, alpha subunit-like effector A (predicted)	3.0
1368223_at	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 1	3.0
1388792_at	growth arrest and DNA-damage-inducible 45 gamma (predicted)	3.0
1389805_at	ESTs	3.0
1387060_at	core promoter element binding protein	3.0

1388628_at	integral type I protein	2.9
1390738_at	DAMP-1 protein	2.9
1390177_at	similar to CDNA sequence BC063749	2.9
1387092_at	FXYD domain-containing ion transport regulator 4	2.9
1373514_at	similar to chromosome 17 open reading frame 27 (predicted)	2.9
1367574_at	vimentin	2.9
1368024_at	quiescin Q6	2.9
1388339_at	phosphoprotein enriched in astrocytes 15 (predicted)	2.9
1367577_at	heat shock 27kDa protein 1	2.9
1372190_at	aquaporin 4	2.9
1367661_at	S100 calcium binding protein A6 (calcyclin)	2.8
1371995_at	similar to Hypothetical protein KIAA0469 (predicted)	2.8
1371055_at	RAB12, member RAS oncogene family	2.8
1387902_a_at	ESTs	2.8
1382076_at	solute carrier family 37 (glycerol-3-phosphate transporter), member 1 (predicted)	2.8
1388459_at	collagen, type XVIII, alpha 1	2.8
1374474_at	copine VIII (predicted)	2.8
1388592_at	claudin 19 (predicted)	2.8
1367570_at	transgelin	2.8
1368519_at	plasminogen activator inhibitor type 1 (PAI-1)	2.8
1389986_at	ESTs	2.8
1389594_at	similar to Protein C20orf22 homolog	2.7
1367973_at	chemokine (C-C motif) ligand 2	2.7
1390391_at	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3	2.7
1367584_at	annexin A2	2.7
1373286_at	CSX-associated LIM	2.7
1372539_at	ESTs	2.6
1389179_at	cell death-inducing DNA fragmentation factor, alpha subunit-like effector A (predicted)	3.0
1368223_at	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 1	3.0
1388792_at	growth arrest and DNA-damage-inducible 45 gamma (predicted)	3.0
1389805_at	ESTs	3.0
1387060_at	core promoter element binding protein	3.0
1388628_at	integral type I protein	2.9
1390738_at	DAMP-1 protein	2.9
1390177_at	similar to CDNA sequence BC063749	2.9
1387092_at	FXYD domain-containing ion transport regulator 4	2.9
1373514_at	similar to chromosome 17 open reading frame 27 (predicted)	2.9
1367786_at	proteosome (prosome, macropain) subunit, beta type 8	2.5
1387906_a_at	GNAS complex locus	2.5
1373035_at	fos-like antigen 2	2.5
1387843_at	follistatin	2.5
1368308_at	myelocytomatosis viral oncogene homolog (avian)	2.4
1387952_a_at	CD44 antigen	2.4
1376977_at	prostaglandin E receptor 3 (subtype EP3)	2.4
1370234_at	fibronectin 1	2.4
1373494_at	breakpoint cluster region (predicted)	2.4
1387854_at	procollagen, type I, alpha 2	2.4
1391509_at	tumor-associated calcium signal transducer 2	2.4
1369964_at	coronin, actin binding protein 1A	2.4
1370896_a_at	similar to Myh11 protein	2.4
1370086_at	fibrinogen, gamma polypeptide	2.4
1368420_at	ceruloplasmin	2.4
1368000_at	complement component 3	2.4
1382680_at	adipose differentiation-related protein	2.4
1373778_at	acetyl-Coenzyme A carboxylase beta	2.4
1388393_at	proteolipid protein 2	2.4
1368254_a_at	sphingosine kinase 1	2.4
1388272_at	immunoglobulin heavy chain 1a (serum IgG2a) (predicted)	2.4
1388846_at	BCL2-like 12 (proline rich) (predicted)	2.4
1373823_at	similar to Cyclin-dependent kinases regulatory subunit 2 (CKS-2)	2.3
1370603_a_at	protein tyrosine phosphatase, receptor type, C	2.3
1390411_at	claudin 19 (predicted)	2.3
1389464_at	ligand of numb-protein X 1 (predicted)	2.3
1387946_at	lectin, galactoside-binding, soluble, 3 binding protein	2.3
1368073_at	interferon regulatory factor 1	2.3
1369527_at	chemokine (C-X3-C) receptor 1	2.3
1389503_at	similar to angiopoietin 1	2.3
1370288_a_at	tropomyosin 1, alpha	2.3
1375170_at	S100 calcium binding protein A11 (calizzarin) (predicted)	2.3

1386921_at	carboxypeptidase E	2.3
1369977_at	ubiquitin carboxy-terminal hydrolase L1	2.3
1388455_at	similar to OTTHUMP00000063926	2.3
1389734_x_at	histocompatibility 2, T region locus 24	2.3
1398394_at	ESTs	2.3
1369437_at	solute carrier organic anion transporter family, member 4a1	2.2
1367862_at	Ras-related associated with diabetes	2.2
1373628_at	ESTs	2.2
1387030_at	ATP-binding cassette, sub-family C (CFTR/MRP), member 5	2.2
1390226_at	ESTs	2.2
1376931_at	similar to Hepatocellular carcinoma-associated antigen 58 homolog (predicted)	2.2
1372290_at	RD RNA-binding protein	2.2
1368205_at	complement factor I	2.2
1370869_at	branched chain aminotransferase 1, cytosolic	2.2
1368871_at	mitogen activated protein kinase kinase kinase 1	2.2
1371989_at	high mobility group nucleosomal binding domain 3	2.2
1374119_at	E74-like factor 3 (predicted)	2.2
1367784_a_at	clusterin	2.2
1368914_at	runt related transcription factor 1	2.2
1368363_at	Kruppel-like factor 5	2.2
1367776_at	cell division cycle 2 homolog A (S. pombe)	2.2
1371349_at	similar to collagen alpha1 type VI-precursor	2.2
1388970_at	Ras interacting protein 1 (predicted)	2.2
1389754_at	preoptic regulatory factor-1	2.2
1370228_at	Transferrin	2.1
1374247_at	stabilin 1 (predicted)	2.1
1388493_at	similar to Expressed sequence AW146242 (predicted)	2.1
1377092_at	suppressor of cytokine signaling 3	2.1
1367745_at	diacylglycerol kinase zeta	2.1
1368732_at	transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)	2.1
1376481_at	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 9 (predicted)	2.1
1374153_at	phosducin-like 3 (predicted)	2.1
1390659_at	CD44 antigen	2.1
1369953_a_at	CD24 antigen	2.1
1389095_at	biregional cell adhesion molecule-related/down-regulated by oncogenes (Cdon) binding protein (predicted)	2.1
1368869_at	A kinase (PRKA) anchor protein (gravin) 12	2.1
1370391_at	cellular retinoic acid binding protein 2	2.1
1390250_x_at	Atpase, class I, type 8B, member 2 (predicted)	2.1
1370854_at	nexilin	2.1
1370376_a_at	cold shock domain protein A	2.1
1370885_at	cathepsin Y	2.1
1375305_at	ESTs	2.1
1372153_at	type I keratin KA15	2.0
1376835_at	solute carrier family 35, member B2	2.0
1367655_at	thymosin, beta 10	2.0
1388193_at	huntingtin interacting protein 1	2.0
1387770_at	interferon, alpha-inducible protein 27-like	2.0
1371079_at	Fc receptor, IgG, low affinity IIb	2.0
1389189_at	actinin, alpha 1	2.0
1372868_at	torsin family 3, member A (predicted)	2.0
1369949_at	Lutheran blood group (Auberger b antigen included)	2.0
1369955_at	collagen, type V, alpha 1	2.0
1386862_at	annexin A5	2.0

AFFY Probe	Gene Name	Down Regulated Fold Change
1368438_at	phosphodiesterase 10A	-2.1
1390014_at	ESTs	-2.2
1375779_at	ESTs	-2.3
1385267_at	ESTs	-2.3
1370222_at	paired-like homeodomain transcription factor 3	-2.5
1390167_at	similar to hypothetical protein FLJ30373 (predicted)	-2.5
1369485_at	cytosolic acetyl-CoA hydrolase	-2.6
1370355_at	stearoyl-Coenzyme A desaturase 1	-20.7

Appendix 2

SHR L-NAME Microarray Gene Expression Fold Changes

AFFY Probe	Gene Name	Upregulated Fold Change
1387965_at	kidney injury molecule 1	42.9
1387908_at	RAS, dexamethasone-induced 1	24.7
1387011_at	lipocalin 2	23.6
1387050_s_at	kininogen 1	23.0
1370992_a_at	fibrinogen, alpha polypeptide	13.5
1368187_at	glycoprotein (transmembrane) nmb	12.4
1368519_at	plasminogen activator inhibitor type 1 (PAI-1)	11.5
1374070_at	glutathione peroxidase 2	11.4
1370177_at	poliovirus receptor	10.6
1370080_at	heme oxygenase (decycling) 1	9.8
1388924_at	angiopoietin-like protein 4	9.3
1369268_at	activating transcription factor 3	8.3
1367581_a_at	secreted phosphoprotein 1 (Osteopontin)	7.9
1388547_at	claudin 4 (predicted)	7.8
1388246_at	clusterin	7.6
1380444_at	minichromosome maintenance deficient 10 (S. cerevisiae) (predicted)	7.5
1367712_at	tissue inhibitor of metalloproteinase 1	7.4
1370113_at	inhibitor of apoptosis protein 1	7.2
1367784_a_at	clusterin	7.1
1389500_at	EST	6.8
1392647_at	serum amyloid A 3 (predicted)	6.7
1373908_at	EST	6.7
1370445_at	phosphatidylserine-specific phospholipase A1	6.4
1393730_at	a disintegrin and metallopeptidase with thrombospondin motifs 4	6.3
1388674_at	cyclin-dependent kinase inhibitor 1A	6.2
1373911_at	EST	6.0
1377163_at	inhibin beta-B	5.8
1370894_at	claudin 7	5.8
1368223_at	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 1	5.7
1368420_at	ceruloplasmin	5.7
1368471_at	guanylate cyclase activator 2A	5.6
1380336_at	interleukin-1 receptor-associated kinase 3 (predicted)	5.5
1397769_at	cathepsin D	5.2
1373787_at	solute carrier family 6 (neurotransmitter transporter, glycine), member 9	5.1
1368921_a_at	CD44 antigen	5.1
1368683_at	oxidized low density lipoprotein (lectin-like) receptor 1	5.1
1397225_at	zinc finger and BTB domain containing 16	5.1
1378015_at	chemokine (C-C motif) ligand 21b (serine) (predicted)	4.8
1368115_at	claudin 3	4.8
1390287_at	bridging integrator 2 (predicted)	4.7
1368168_at	solute carrier family 34 (sodium phosphate), member 2	4.6
1390364_at	runt related transcription factor 1	4.6
1392648_at	mannose receptor, C type 1 (predicted)	4.6
1370310_at	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2	4.6
1380611_at	FK506 binding protein 5 (predicted)	4.5
1371785_at	tumor necrosis factor receptor superfamily, member 12a	4.4
1390839_at	similar to RIKEN cDNA E030024M05 (predicted)	4.4
1367584_at	annexin A2	4.3
1368128_at	phospholipase A2, group IIA (platelets, synovial fluid)	4.2
1386879_at	lectin, galactose binding, soluble 3	4.2
1368540_at	trophoblast glycoprotein	4.2
1367985_at	aminolevulinic acid synthase 2	4.2
1380028_at	EST	4.2
1370892_at	complement component 4a	4.1
1387659_at	guanine deaminase	4.1
1387952_a_at	CD44 antigen	4.1
1373286_at	CSX-associated LIM	4.0
1386890_at	S100 calcium binding protein A10 (calpactin)	4.0
1374784_at	phosphoribosyl transferase domain containing 1 (predicted)	4.0
1367914_at	epithelial membrane protein 3	3.9
1388485_at	chemokine (C-X-C motif) ligand 14 (predicted)	3.9
1392012_at	EST	3.9
1393917_at	CD163 antigen (predicted)	3.8
1391106_at	oncostatin M specific receptor	3.8
1387273_at	interleukin 1 receptor-like 1	3.8
1392264_s_at	plasminogen activator inhibitor type 1 (PAI-1)	3.8

1387306_a_at	early growth response 2	3.8
1377639_at	visceral adipose tissue-specific transmembrane protein OL-16	3.8
1368448_at	latent transforming growth factor beta binding protein 2	3.8
1370807_at	vacuole Membrane Protein 1	3.8
1392613_at	zinc finger and BTB domain containing 16	3.8
1370967_at	similar to productively rearranged V-lambda-2	3.7
1376109_at	iGb3 synthase	3.6
1379914_at	transcription factor CP2-like 2 (predicted)	3.6
1374806_at	similar to 14-3-3 protein sigma	3.6
1392899_at	protein regulator of cytokinesis 1 (predicted)	3.6
1376390_at	membrane-spanning 4-domains, subfamily A, member 11 (predicted)	3.6
1371245_a_at	hemoglobin beta chain complex	3.6
1379716_at	CD163 antigen (predicted)	3.6
1375972_at	similar to membrane protein expressed in epithelial-like lung adenocarcinoma (predicted)	3.5
1370563_at	3-alpha-hydroxysteroid dehydrogenase	3.5
1373025_at	complement component 1, q subcomponent, gamma polypeptide (predicted)	3.5
1368300_at	adenosine A2a receptor	3.5
1374160_at	EST	3.5
1373363_at	EST	3.5
1372516_at	kinesin family member 22 (predicted)	3.5
1382311_at	TRAF2 binding protein	3.4
1383880_at	integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51) (predicted)	3.4
1387060_at	core promoter element binding protein	3.4
1391187_at	periplakin (predicted)	3.4
1378032_at	similar to molecule possessing ankyrin-repeats induced by lipopolysaccharide; IkappaB-zeta (predicted)	3.3
1398482_at	B-cell leukemia/lymphoma 3 (predicted)	3.3
1367749_at	lumican	3.3
1389123_at	chemokine (C-C motif) ligand 6	3.3
1368160_at	insulin-like growth factor binding protein 1	3.3
1368990_at	cytochrome P450, family 1, subfamily b, polypeptide 1	3.3
1368171_at	lysyl oxidase	3.3
1368172_a_at	lysyl oxidase	3.3
1379248_at	prolylcarboxypeptidase (angiotensinase C) (predicted)	3.3
1373421_at	TG interacting factor (predicted)	3.2
1367768_at	latexin	3.2
1376102_at	similar to RECS1	3.2
1376198_at	visceral adipose tissue-specific transmembrane protein OL-16	3.2
1368505_at	regulator of G-protein signaling 4	3.2
1383486_at	EST	3.2
1368418_a_at	ceruloplasmin	3.2
1395442_at	runt related transcription factor 1	3.2
1372691_at	uridine phosphorylase 1 (predicted)	3.2
1396472_at	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-like 2 (predicted)	3.1
1376496_at	similar to RIKEN cDNA 2310016F22	3.1
1378480_at	cadherin 6	3.1
1388901_at	FK506 binding protein 5 (predicted)	3.1
1368007_at	deleted in malignant brain tumors 1	3.1
1386985_at	glutathione S-transferase, mu 1	3.1
1371250_at	platelet factor 4	3.1
1376976_at	secreted and transmembrane 1	3.1
1368000_at	complement component 3	3.1
1392580_at	EST	3.1
1397719_at	EST	3.1
1388666_at	ectodermal-neural cortex 1	3.1
1386581_at	integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51) (predicted)	3.1
1388944_at	EST	3.0
1386123_at	gap junction membrane channel protein alpha 9	3.0
1368190_at	renin 1	3.0
1385706_at	EST	3.0
1373661_a_at	chemokine (C-X-C motif) receptor 4	3.0
1388339_at	phosphoprotein enriched in astrocytes 15 (predicted)	3.0
1368799_at	baculoviral IAP repeat-containing 5	2.9
1390510_at	membrane-spanning 4-domains, subfamily A, member 6B	2.9
1383355_at	ATP-binding cassette, sub-family A (ABC1), member 1	2.9
1374540_at	cell division cycle associated 7 (predicted)	2.9
1385190_at	gamma-aminobutyric acid (GABA) A receptor, pi	2.9
1389244_x_at	chemokine (C-X-C motif) receptor 4	2.9
1389659_at	similar to ctla-2-beta protein (141 AA)	2.9
1388393_at	proteolipid protein 2	2.9
1389096_at	similar to flavoprotein oxidoreductase MICAL2 (predicted)	2.9

1384707_at	similar to RIKEN cDNA 4933425F03 (predicted)	2.9
1370341_at	enolase 2, gamma	2.9
1394028_at	dual specificity phosphatase 10 (predicted)	2.9
1382896_at	similar to C-terminal tensin-like (predicted)	2.9
1368464_at	macrophage galactose N-acetyl-galactosamine specific lectin 1	2.9
1391925_at	chemokine (C-C motif) ligand 19 (predicted)	2.9
1373401_at	tenascin C	2.9
1390672_at	EST	2.8
1387253_at	guanylate cyclase activator 2b	2.8
1390520_at	EST	2.8
1375170_at	S100 calcium binding protein A11 (calizzarin) (predicted)	2.8
1379614_at	cadherin 6	2.8
1374535_at	similar to expressed sequence AU041783 (predicted)	2.8
1373035_at	fos-like antigen 2	2.8
1378056_at	geminin (predicted)	2.8
1393413_at	similar to RIKEN cDNA 9430031J16 (predicted)	2.8
1389253_at	vanin 1 (predicted)	2.8
1386994_at	B-cell translocation gene 2, anti-proliferative	2.7
1372011_at	guanine deaminase	2.7
1369720_at	myosin Ib	2.7
1395603_at	EST	2.7
1374670_at	similar to hypothetical protein MGC20700 (predicted)	2.7
1372256_at	EST	2.7
1368490_at	CD14 antigen	2.7
1372603_at	protein kinase C and casein kinase substrate in neurons 3 (predicted)	2.7
1371537_at	UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 5 (predicted)	2.7
1368869_at	A kinase (PRKA) anchor protein (gravin) 12	2.7
1374306_at	similar to 14-3-3 protein sigma	2.7
1370034_at	cell division cycle 25 homolog B (S. cerevisiae)	2.7
1379613_at	similar to hypothetical protein MGC29390 (predicted)	2.7
1380621_at	feline sarcoma oncogene (predicted)	2.7
1376356_a_at	bridging integrator 2 (predicted)	2.7
1397471_at	EST	2.7
1395468_at	discs, large homolog 4 (Drosophila)	2.7
1392762_at	EST	2.7
1368480_at	CDW92 antigen	2.7
1380909_at	solute carrier family 25 (mitochondrial carrier, phosphate carrier), member 24 (predicted)	2.6
1392800_at	similar to hypothetical protein MGC17337 (predicted)	2.6
1388116_at	collagen, type 1, alpha 1	2.6
1388460_at	capping protein (actin filament), gelsolin-like (predicted)	2.6
1370215_at	complement component 1, q subcomponent, beta polypeptide	2.6
1379656_a_at	coronin, actin binding protein 2A (predicted)	2.6
1376708_at	similar to hypothetical protein MGC7793 (predicted)	2.6
1385925_at	EST	2.6
1378074_at	pyruvate dehydrogenase kinase, isoenzyme 4	2.6
1388939_at	procollagen, type XV (predicted)	2.6
1395557_at	core promoter element binding protein	2.6
1370693_a_at	cyclic nucleotide phosphodiesterase 1	2.6
1368983_at	diphtheria toxin receptor	2.6
1374280_at	cerebellin 2 precursor protein (predicted)	2.6
1385047_x_at	similar to cell surface receptor FDFACT	2.5
1386888_at	eukaryotic translation initiation factor 4E binding protein 1	2.5
1376513_a_at	EST	2.5
1384532_at	calpain 5	2.5
1382395_at	EST	2.5
1374474_at	copine VIII (predicted)	2.5
1383286_at	pleckstrin 2 (predicted)	2.5
1387260_at	Kruppel-like factor 4 (gut)	2.5
1382218_at	EST	2.5
1398294_at	actinin, alpha 1	2.5
1387322_at	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6B	2.5
1382192_at	extra cellular link domain-containing 1 (predicted)	2.5
1371691_at	retinoic acid receptor responder (tazarotene induced) 2 (predicted)	2.5
1367715_at	tumor necrosis factor receptor superfamily, member 1a	2.5
1367974_at	annexin A3	2.5
1370258_at	basic leucine zipper and W2 domains 2	2.5
1376688_a_at	zinc finger, CW-type with PWWP domain 1 (predicted)	2.5
1386987_at	interleukin 6 receptor	2.5
1388650_at	hypothetical protein LOC29390	2.5
1387892_at	tubulin, beta 5	2.5

1367998_at	secretory leukocyte peptidase inhibitor	2.5
1367661_at	S100 calcium binding protein A6 (calcyclin)	2.5
1374620_at	CEA-related cell adhesion molecule 1	2.5
1393706_at	six transmembrane epithelial antigen of the prostate (predicted)	2.5
1382730_at	EST	2.5
1384449_at	EST	2.5
1368608_at	cytochrome P450, family 2, subfamily f, polypeptide 2	2.5
1380088_at	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 12 (predicted)	2.5
1367805_at	glutaminase	2.5
1367655_at	thymosin, beta 10	2.4
1367806_at	glutaminase	2.4
1382351_at	GTP binding protein (gene overexpressed in skeletal muscle) (predicted)	2.4
1380410_at	GLI pathogenesis-related 2 (predicted)	2.4
1395357_at	microtubule-associated protein 1b	2.4
1368650_at	TGFB inducible early growth response	2.4
1389408_at	similar to M2 ribonucleotide reductase	2.4
1375010_at	CD68 antigen (predicted)	2.4
1382710_at	EST	2.4
1394954_at	solute carrier family 31, member 2 (predicted)	2.4
1371530_at	keratin complex 2, basic, gene 8	2.4
1373554_at	similar to SPRY domain-containing SOCS box protein SSB-1 (predicted)	2.4
1382142_at	NIPSNAP-related protein	2.4
1379957_at	similar to schlafen 8	2.4
1367614_at	annexin A1	2.4
1392578_at	matrix Gla protein	2.4
1386925_at	actin related protein 2/3 complex, subunit 1B	2.4
1386941_at	plectin 1	2.4
1379356_at	similar to RIKEN cDNA C230093N12 (predicted)	2.4
1383401_at	similar to Testis derived transcript	2.4
1398246_s_at	Fc receptor, IgG, low affinity III	2.4
1374228_at	tripartite motif protein 47 (predicted)	2.4
1380696_at	similar to RIKEN cDNA C230093N12 (predicted)	2.4
1391206_at	similar to hypothetical protein FLJ10901 (predicted)	2.4
1369150_at	pyruvate dehydrogenase kinase, isoenzyme 4	2.4
1370347_at	PDZ and LIM domain 7	2.4
1388985_at	EST	2.4
1388986_at	core promoter element binding protein	2.4
1370813_at	glutathione S-transferase, mu 5	2.4
1389368_at	membrane associated guanylate kinase interacting protein-like 1 (predicted)	2.4
1388143_at	collagen, type XVIII, alpha 1	2.4
1368419_at	ceruloplasmin	2.4
1387897_at	cyclic nucleotide phosphodiesterase 1	2.4
1387925_at	asparagine synthetase	2.4
1374033_at	proteasome (prosome, macropain) subunit, beta type 10 (predicted)	2.4
1385926_at	GLI pathogenesis-related 2 (predicted)	2.4
1377994_at	phorbol-12-myristate-13-acetate-induced protein 1	2.4
1380229_at	v-maf musculoaponeurotic fibrosarcoma oncogene family, protein F (avian) (predicted)	2.4
1389071_at	EST	2.3
1372186_a_at	hypothetical protein LOC29390	2.3
1390507_at	interferon-stimulated protein (predicted)	2.3
1372653_at	FK506 binding protein 11 (predicted)	2.3
1385961_at	EST	2.3
1371382_at	similar to Filamin A (Alpha-filamin) (Filamin 1) (Endothelial actin-binding protein) (Actin-binding protein 280)	2.3
1393688_at	similar to cell surface receptor FDFACT	2.3
1374699_at	similar to NSE1 (predicted)	2.3
1371071_at	EST	2.3
1368497_at	ATP-binding cassette, sub-family C (CFTR/MRP), member 2	2.3
1377886_at	tripartite motif protein 6 (predicted)	2.3
1372844_at	ephrin A1	2.3
1369947_at	cathepsin K	2.3
1368790_at	serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 10	2.3
1394039_at	Kruppel-like factor 5	2.3
1368006_at	lysosomal-associated protein transmembrane 5	2.3
1385702_at	myeloid cell nuclear differentiation antigen (predicted)	2.3
1393401_at	EST	2.3
1398347_at	AXL receptor tyrosine kinase (predicted)	2.3
1370657_at	cadherin 6	2.3
1371349_at	similar to collagen alpha1 type VI-precursor	2.3
1372729_at	protein C receptor, endothelial (predicted)	2.3
1397164_at	similar to RIKEN cDNA 1200004M23 (predicted)	2.3

1373780_at	tetraspan 1	2.3
1384174_at	EST	2.3
1388392_at	Tax1 (human T-cell leukemia virus type I) binding protein 3 (predicted)	2.3
1382955_at	G protein-coupled receptor 126 (predicted)	2.3
1383940_at	cell division cycle associated 1 (predicted)	2.3
1389355_at	immediate early response 5	2.3
1382590_at	similar to RIKEN cDNA 2310015N21	2.3
1389103_at	similar to RIKEN cDNA 2810037C03 (predicted)	2.3
1383797_a_at	torsin family 2, member A	2.3
1378140_at	ADP-ribosylation factor-like 11 (predicted)	2.3
1387343_at	CCAAT/enhancer binding protein (C/EBP), delta	2.3
1384310_at	phosphodiesterase 5A, cGMP-specific	2.3
1368669_at	uncoupling protein 2	2.2
1367574_at	vimentin	2.2
1397904_at	EST	2.2
1376645_at	similar to RIKEN cDNA 6330406I15 (predicted)	2.2
1370153_at	growth differentiation factor 15	2.2
1373473_a_at	nucleosome assembly protein 1-like 1	2.2
1389409_at	similar to Testis derived transcript	2.2
1383874_at	LOC500640	2.2
1374119_at	E74-like factor 3 (predicted)	2.2
1380363_at	Kruppel-like factor 7 (ubiquitous) (predicted)	2.2
1384507_at	EST	2.2
1371102_x_at	hemoglobin beta chain complex	2.2
1392894_at	fibrinogen-like 2	2.2
1386956_at	scavenger receptor class B, member 1	2.2
1372389_at	similar to immediate early response 2	2.2
1371369_at	procollagen, type VI, alpha 2 (predicted)	2.2
1379295_at	phosphatase, orphan 1 (predicted)	2.2
1393095_at	tankyrase 1 binding protein 1 (predicted)	2.2
1398706_at	EST	2.2
1370234_at	fibronectin 1	2.2
1368207_at	FXYD domain-containing ion transport regulator 5	2.2
1376816_at	breast cancer 1	2.2
1397167_at	EST	2.2
1397317_at	EST	2.2
1380450_at	similar to hypothetical protein FLJ20315 (predicted)	2.2
1383578_at	similar to DNA repair protein RAD51 homolog 1	2.2
1368895_at	neuroligin 2	2.2
1392922_at	RAP2B, member of RAS oncogene family	2.2
1374247_at	stabilin 1 (predicted)	2.2
1373368_at	EST	2.2
1382774_at	paternally expressed 12 (predicted)	2.2
1394779_at	EST	2.2
1378076_at	EST	2.2
1371923_at	EST	2.2
1370959_at	collagen, type III, alpha 1	2.2
1372042_at	chemokine-like factor super family 3 (predicted)	2.2
1377340_at	tissue factor pathway inhibitor 2	2.2
1388742_at	BCL2-like 11 (apoptosis facilitator)	2.2
1374157_at	phosphodiesterase 4B	2.2
1384400_at	similar to KIAA1683	2.2
1386396_at	dual specificity phosphatase 8 (predicted)	2.2
1385649_at	integrin alpha 5	2.2
1383641_at	endothelin receptor type A	2.2
1376055_at	minichromosome maintenance deficient 5, cell division cycle 46 (S. cerevisiae) (predicted)	2.1
1373204_at	hypothetical LOC297077 (predicted)	2.1
1372931_at	similar to DXImx39e protein	2.1
1368143_at	annexin A7	2.1
1367973_at	chemokine (C-C motif) ligand 2	2.1
1382631_at	similar to SPT3-associated factor 42 (predicted)	2.1
1390547_at	sialyltransferase 7 ((alpha-N-acetylneuraminyl 2,3-beta-galactosyl-1,3)-N-acetyl galactosaminde alpha-2,6-sialyltransferase)	2.1
1386568_at	interferon regulatory factor 6 (predicted)	2.1
1384934_at	solute carrier family 41, member 2 (predicted)	2.1
1392927_at	progestin and adipoQ receptor family member IV (predicted)	2.1
1391830_at	copine VIII (predicted)	2.1
1392755_at	similar to hypothetical protein AD158 (predicted)	2.1
1390946_at	runt-related transcription factor 3	2.1
1380257_at	SMC5 structural maintenance of chromosomes 5-like 1 (yeast) (predicted)	2.1
1371432_at	vesicle amine transport protein 1 homolog (T californica) (predicted)	2.1

1388876_at	phospholamban	2.1
1371450_at	EST	2.1
1389425_at	EST	2.1
1370895_at	collagen, type V, alpha 2	2.1
1377669_at	low Mr GTP-binding protein	2.1
1391063_at	kinesin family member 23 (predicted)	2.1
1385851_at	calpain 5	2.1
1370864_at	collagen, type 1, alpha 1	2.1
1375633_at	chloride intracellular channel 1	2.1
1393048_at	EST	2.1
1367577_at	heat shock 27kDa protein 1	2.1
1382431_at	ATP-binding cassette, sub-family A (ABC1), member 1	2.1
1367850_at	Fc receptor, IgG, low affinity III	2.1
1376998_a_at	similar to FLJ00128 protein (predicted)	2.1
1393641_at	similar to SH2-containing leukocyte protein 65	2.1
1388729_at	Harvey rat sarcoma oncogene, subgroup R (predicted)	2.1
1391383_at	cartilage acidic protein 1	2.1
1372868_at	torsin family 3, member A (predicted)	2.1
1394483_at	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 5 (aggrecanase-2)	2.1
1392794_at	EST	2.1
1391139_at	similar to hypothetical protein 5930437A14 (predicted)	2.1
1368838_at	tropomyosin 4	2.1
1385761_s_at	EST	2.1
1398108_at	Rho GDP dissociation inhibitor (GDI) alpha	2.1
1373984_at	solute carrier family 39 (zinc transporter), member 14 (predicted)	2.1
1395388_at	EST	2.1
1396150_at	claudin 1	2.1
1395039_at	solute carrier organic anion transporter family, member 3a1	2.1
1370313_at	brain acyl-CoA hydrolase	2.1
1389706_at	activity and neurotransmitter-induced early gene protein 4 (ania-4)	2.1
1373979_at	EST	2.1
1372510_at	neoplastic progression 3 (predicted)	2.1
1387605_at	caspase 12	2.1
1382751_at	WAP four-disulfide core domain 10A (predicted)	2.0
1392531_at	EST	2.0
1389503_at	similar to angiopoietin 1	2.0
1369956_at	interferon gamma receptor 1	2.0
1373504_at	GLI pathogenesis-related 1 (glioma) (predicted)	2.0
1391932_at	similar to hypothetical protein MGC47256 (predicted)	2.0
1395072_at	similar to hypothetical protein FLJ10901 (predicted)	2.0
1367650_at	lipocalin 7	2.0
1389282_at	integrin alpha 3 (predicted)	2.0
1375862_at	similar to mKIAA0230 protein	2.0
1382087_at	EST	2.0
1370228_at	Transferrin	2.0
1384035_at	similar to SPT3-associated factor 42 (predicted)	2.0
1390931_at	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 15 (predicted)	2.0
1368518_at	CD53 antigen	2.0
1390692_at	cytidine 5'-triphosphate synthase (predicted)	2.0
1377814_at	EST	2.0
1373928_at	similar to interleukin 17 receptor E isoform 1	2.0
1392389_at	fatty acid 2-hydroxylase (predicted)	2.0
1370826_at	nucleosome assembly protein 1-like 1	2.0
1372559_at	Ng23 protein	2.0
1391808_at	EST	2.0
1371073_at	UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 1	2.0
1389618_at	F-box only protein 32	2.0
1370019_at	sulfotransferase family 1A, phenol-preferring, member 1	2.0
1393618_at	similar to CDNA sequence BC027309	2.0
1377944_at	similar to cellular repressor of E1A-stimulated genes 2	2.0
1376652_at	complement component 1, q subcomponent, alpha polypeptide (predicted)	2.0
1368142_at	annexin A7	2.0
1369963_at	platelet-activating factor acetylhydrolase, isoform 1b, alpha1 subunit	2.0
1388138_at	thrombospondin 4	2.0
1369197_at	apoptotic peptidase activating factor 1	2.0
1383688_at	EST	2.0
1397798_at	EST	2.0
1370239_at	hemoglobin alpha, adult chain 1	2.0

Down-regulated

AFFY Probe	Gene Name	Fold Change
1387265_at	diacylglycerol kinase, gamma	-2.0
1370547_at	pregnancy-zone protein	-2.0
1378191_at	nuclear cap binding protein subunit 1, 80kDa (predicted)	-2.0
1387941_s_at	phospholipase A2, group VI	-2.0
1367835_at	proprotein convertase subtilisin/kexin type 1 inhibitor	-2.0
1370688_at	glutamate-cysteine ligase, catalytic subunit	-2.0
1391417_at	similar to betaine-homocysteine methyltransferase 2	-2.0
1393507_at	EST	-2.0
1368249_at	Kruppel-like factor 15	-2.0
1374959_at	NAD(P)H dehydrogenase, quinone 2	-2.0
1396246_at	similar to DNA segment, Chr 10, ERATO Doi 214, expressed (predicted)	-2.0
1380045_at	pyruvate dehydrogenase phosphatase isoenzyme 2	-2.0
1381973_at	solute carrier family 25, member 30	-2.0
1386212_at	spectrin alpha 1 (predicted)	-2.0
1385574_at	similar to cDNA sequence AF397014 (predicted)	-2.0
1389392_at	chloride channel 6 (predicted)	-2.0
1381176_at	ubiquinol-cytochrome c reductase core protein II	-2.0
1387812_at	Subtilisin - like endoprotease	-2.0
1384874_at	EST	-2.0
1397871_at	transient receptor protein 5	-2.0
1382599_at	insulin-like growth factor 1	-2.0
1398295_at	solute carrier family 29 (nucleoside transporters), member 1	-2.0
1375932_at	phosphoribosyl pyrophosphate synthetase 2	-2.0
1378773_at	ciliary rootlet coiled-coil, rootletin (predicted)	-2.0
1368208_at	camello-like 1	-2.1
1387347_at	insulin-like growth factor binding protein 5	-2.1
1383826_at	Rab40b, member RAS oncogene family (predicted)	-2.1
1391652_at	glycine-N-acyltransferase (predicted)	-2.1
1382569_at	progestin and adipoQ receptor family member IX (predicted)	-2.1
1372449_at	solute carrier family 8 (sodium/calcium exchanger), member 1	-2.1
1379418_at	EST	-2.1
1385620_at	heat shock protein 105 (predicted)	-2.1
1388172_at	putative integral membrane transport UST1r	-2.1
1389744_at	LOC499898	-2.1
1387672_at	glycine N-methyltransferase	-2.1
1370072_at	membrane metallo endopeptidase	-2.1
1396229_at	EST	-2.1
1375729_at	similar to Eph receptor A4	-2.1
1377993_at	guanine nucleotide binding protein 13, gamma (predicted)	-2.1
1394611_at	similar to acyloxyacyl hydrolase	-2.1
1386648_at	DnaJ (Hsp40) homolog, subfamily C, member 6 (predicted)	-2.1
1369158_at	calcium-sensing receptor	-2.1
1374524_at	selenocysteine lyase	-2.1
1390851_at	lactamase, beta 2 (predicted)	-2.1
1377033_at	serine (or cysteine) proteinase inhibitor, clade F, member 2 (predicted)	-2.1
1378819_at	similar to RIKEN cDNA 0610012D14 (predicted)	-2.1
1386720_at	transmembrane protease, serine 8 (intestinal)	-2.1
1373218_at	similar to 6430514L14Rik protein (predicted)	-2.1
1378292_at	EST	-2.1
1369493_at	prolactin receptor	-2.1
1392411_at	tubulointerstitial nephritis antigen	-2.1
1385375_at	EST	-2.1
1391147_at	EST	-2.1
1384855_at	similar to RIKEN cDNA 1700009P17	-2.1
1383760_at	EST	-2.1
1370566_at	retinol dehydrogenase type II (RODH II)	-2.1
1397287_at	similar to 4931417G12Rik protein	-2.1
1384215_at	M-phase phosphoprotein 9 (predicted)	-2.1
1371643_at	cyclin D2	-2.1
1395032_at	similar to RIKEN cDNA E130308A19 (predicted)	-2.1
1368164_at	biliverdin reductase A	-2.1
1386054_at	EST	-2.1
1385383_at	similar to hypothetical protein 4933409I22	-2.1
1370259_a_at	parathyroid hormone receptor 1	-2.1
1398107_at	similar to RIKEN cDNA A030007L17; EST AA673177 (predicted)	-2.1
1374217_at	similar to chromosome 16 open reading frame 5 (predicted)	-2.1
1368313_a_at	transient receptor potential cation channel, subfamily V, member 1	-2.1
1369491_at	D-amino acid oxidase	-2.1
1370981_at	retinoid X receptor gamma	-2.1

1380013_at	adiponutrin (predicted)	-2.2
1382034_at	aldo-keto reductase family 1, member B10 (aldose reductase) (predicted)	-2.2
1368325_at	epidermal growth factor	-2.2
1367909_at	dicarbonyl L-xylulose reductase	-2.2
1374963_s_at	EST	-2.2
1386969_at	neuritin	-2.2
1375030_at	UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 5 (predicted)	-2.2
1394020_at	solute carrier family 16 (monocarboxylic acid transporters), member 7	-2.2
1392809_at	EST	-2.2
1385724_at	similar to RIKEN cDNA 4122402O22 (predicted)	-2.2
1396095_at	EST	-2.2
1390598_at	glial cells missing homolog 1 (Drosophila)	-2.2
1371266_at	afamin	-2.2
1379885_at	flavin containing monooxygenase 4	-2.2
1395411_at	nicotinate phosphoribosyltransferase-like protein	-2.2
1377135_at	EST	-2.2
1369401_at	solute carrier family 21, member 13	-2.2
1392145_at	EST	-2.2
1369100_at	angiotensin/vasopressin receptor	-2.2
1381618_at	EST	-2.2
1394594_at	similar to mKIAA1244 protein (predicted)	-2.2
1376709_at	solute carrier family 39 (metal ion transporter), member 8 (predicted)	-2.2
1384499_at	butyryl Coenzyme A synthetase 1 (predicted)	-2.2
1382061_at	lactate dehydrogenase D (predicted)	-2.2
1382211_at	membrane metallo endopeptidase	-2.2
1378245_at	similar to 6430514L14Rik protein (predicted)	-2.2
1377672_at	EST	-2.2
1392569_at	insulin-like growth factor 1	-2.2
1379587_at	EST	-2.2
1379518_at	EST	-2.2
1369531_at	similar to Sulfotransferase K1 (rSULT1C2)	-2.2
1398507_at	EST	-2.2
1379848_at	EST	-2.2
1384964_at	EST	-2.2
1392521_at	EST	-2.2
1376078_at	hypothetical gene supported by BC088439	-2.2
1378896_at	solute carrier family 30 (zinc transporter), member 2	-2.2
1367951_at	phosphoglycerate mutase 2	-2.2
1372976_at	similar to Dorz1 (predicted)	-2.2
1377155_at	Camello-like 2	-2.2
1378288_at	similar to RIKEN cDNA D630035O19 (predicted)	-2.2
1369254_a_at	prostaglandin E receptor 1	-2.2
1370853_at	CaM-kinase II inhibitor alpha	-2.3
1383111_at	2-amino-3-carboxymuconate-6-semialdehyde decarboxylase	-2.3
1382918_at	EST	-2.3
1384838_at	solute carrier family 34 (sodium phosphate), member 3	-2.3
1381655_at	similar to expressed sequence AW121567	-2.3
1370816_at	nuclear receptor subfamily 1, group D, member 1	-2.3
1371643_at	cyclin D1	-2.3
1383390_at	similar to hypothetical protein FLJ25477 isoform 2	-2.3
1383654_a_at	similar to fructosamine-3-kinase	-2.3
1372240_at	sarcoglycan, alpha (dystrophin-associated glycoprotein) (predicted)	-2.3
1383086_at	potassium inwardly-rectifying channel, subfamily J, member 10	-2.3
1385729_at	similar to RIKEN cDNA B230308G19 (predicted)	-2.3
1389166_at	calcium and integrin binding family member 2 (predicted)	-2.3
1376518_at	EST	-2.3
1384202_at	similar to Tescalcin	-2.3
1397855_at	EST	-2.3
1367917_at	cytochrome P450, family 2, subfamily d, polypeptide 26	-2.3
1383838_at	solute carrier family 19, member 3 (predicted)	-2.4
1382969_at	cytomatrix protein p110	-2.4
1389745_at	EST	-2.4
1368304_at	flavin containing monooxygenase 3	-2.4
1391629_at	EST	-2.4
1384603_at	ATP-binding cassette, sub-family A (ABC1), member 4 (predicted)	-2.4
1390656_at	membrane metallo endopeptidase	-2.4
1393508_at	NADPH oxidase 4	-2.4
1375926_at	collagen, type IV, alpha 3	-2.4
1380786_at	SNAP25-interacting protein	-2.4
1376944_at	prolactin receptor	-2.4

1375057_at	similar to Hypothetical protein 6720430O15	-2.4
1381233_at	calcium channel, voltage-dependent, gamma subunit 5	-2.4
1387364_at	folate hydrolase	-2.4
1376141_at	EST	-2.4
1369292_at	hydroxysteroid (17-beta) dehydrogenase 1	-2.4
1396238_at	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 14 (predicted)	-2.4
1390943_at	similar to hypothetical protein dJ465N24.2.1	-2.5
1377333_at	cytomatrix protein p110	-2.5
1373749_at	EST	-2.5
1398612_at	aldo-keto reductase family 1, member C12 (predicted)	-2.5
1369361_at	Klotho	-2.5
1376955_at	procollagen, type IV, alpha 4 (predicted)	-2.5
1376746_at	lactate dehydrogenase D (predicted)	-2.5
1368894_at	CAP, adenylate cyclase-associated protein, 2 (yeast)	-2.5
1370789_a_at	prolactin receptor	-2.5
1374624_at	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 11 (GalNAc-T11)	-2.5
1384529_at	EST	-2.5
1369318_at	fragile histidine triad gene	-2.5
1397615_at	FAT tumor suppressor homolog 3 (Drosophila)	-2.5
1370522_at	glucagon receptor	-2.5
1368139_s_at	alkaline phosphatase, tissue-nonspecific	-2.5
1383943_at	EST	-2.6
1394090_at	EST	-2.6
1395027_at	similar to RIKEN cDNA A030007L17; EST AA673177 (predicted)	-2.6
1385749_at	mitogen activated protein kinase 10	-2.6
1386120_at	EST	-2.6
1368543_at	NADPH oxidase 4	-2.6
1370167_at	syndecan 2	-2.6
1391056_at	aldo-keto reductase family 1, member C12 (predicted)	-2.6
1382742_at	peroxisomal trans-2-enoyl-CoA reductase	-2.6
1387158_at	meprin 1 beta	-2.6
1392612_at	prolactin receptor	-2.6
1373110_at	estrogen receptor 1	-2.6
1386045_at	EST	-2.6
1391544_at	adiponutrin (predicted)	-2.6
1379464_at	calbindin 1	-2.6
1396113_at	similar to Dorz1 (predicted)	-2.6
1396127_at	EST	-2.6
1381310_at	similar to ubiquitin associated protein	-2.6
1383605_at	similar to alpha-fetoprotein	-2.6
1369677_at	cannabinoid receptor 1 (brain)	-2.6
1368145_at	Purkinje cell protein 4	-2.6
1393514_at	EST	-2.7
1378136_at	low density lipoprotein receptor-related protein 3	-2.7
1377018_at	similar to E430002G05Rik protein (predicted)	-2.7
1392825_at	EST	-2.7
1398275_at	matrix metallopeptidase 9	-2.7
1367775_at	alpha-methylacyl-CoA racemase	-2.7
1378307_at	pleckstrin homology domain containing, family H (with MyTH4 domain) member 1 (predicted)	-2.7
1369407_at	tumor necrosis factor receptor superfamily, member 11b (osteoprotegerin)	-2.7
1370456_at	FAT tumor suppressor homolog 3 (Drosophila)	-2.7
1397130_at	mitogen activated protein kinase 10	-2.8
1386938_at	alanyl (membrane) aminopeptidase	-2.8
1384614_at	EST	-2.8
1368366_at	Camello-like 2	-2.8
1382487_at	testis expressed gene 14 (predicted)	-2.8
1387765_at	mannose binding lectin 2, protein C	-2.8
1373309_at	similar to RIKEN cDNA 1810054O13 (predicted)	-2.8
1387382_at	histamine N-methyltransferase	-2.8
1388545_at	EST	-2.8
1370517_at	neuronal pentraxin 1	-2.9
1370675_at	transient receptor potential cation channel, subfamily V, member 1	-2.9
1387363_at	folate hydrolase	-2.9
1382132_at	gamma-aminobutyric acid receptor, subunit beta 3	-2.9
1380962_at	angiotensin I converting enzyme (peptidyl-dipeptidase A) 2	-2.9
1389694_at	kyphoscoliosis (predicted)	-2.9
1391691_at	EST	-2.9
1392457_x_at	EST	-2.9
1390998_at	GLIS family zinc finger 1 (predicted)	-2.9
1390092_at	mitogen-activated protein kinase 4	-2.9

1370147_at	2-amino-3-carboxymuconate-6-semialdehyde decarboxylase	-3.0
1376913_at	beta-1,3-glucuronyltransferase 1 (glucuronosyltransferase P)	-3.0
1372869_at	EST	-3.0
1371137_at	acyl-Coenzyme A oxidase 2, branched chain	-3.0
1371147_at	serine (or cysteine) proteinase inhibitor, clade A, member 3M	-3.0
1393061_at	similar to cDNA sequence BC021608	-3.1
1394484_at	EST	-3.1
1368288_at	group specific component	-3.1
1383412_at	EST	-3.1
1382496_at	hepatocyte nuclear factor 4, alpha	-3.1
1370538_at	laminin, alpha 3	-3.1
1389756_at	maternal embryonic leucine zipper kinase (predicted)	-3.1
1393821_at	EST	-3.1
1383472_at	aldehyde dehydrogenase 1 family, member B1 (predicted)	-3.2
1383014_at	protein kinase, cGMP-dependent, type II	-3.2
1370610_at	solute carrier family 34 (sodium phosphate), member 1	-3.2
1367707_at	fatty acid synthase	-3.2
1382683_a_at	EST	-3.2
1391047_at	EST	-3.2
1388973_at	procollagen, type IX, alpha 1 (predicted)	-3.3
1368289_at	group specific component	-3.3
1385994_at	sporulation protein, meiosis-specific, SPO11 homolog (S. cerevisiae) (predicted)	-3.4
1377086_at	EST	-3.4
1391485_at	EST	-3.4
1369492_at	arylacetamide deacetylase (esterase)	-3.4
1381951_at	EST	-3.5
1370144_at	G protein-binding protein CRFG	-3.5
1387567_at	solute carrier family 21, member 1	-3.6
1380115_at	EST	-3.6
1379445_at	solute carrier family 8 (sodium/calcium exchanger), member 1	-3.6
1378247_at	ELL associated factor 2	-3.6
1380567_at	RNA polymerase 1-4	-3.7
1372911_at	5,10-methylenetetrahydrofolate reductase (NADPH) (predicted)	-3.8
1384960_at	cystic fibrosis transmembrane conductance regulator homolog	-3.8
1389234_at	von Willebrand factor	-4.1
1368779_a_at	guanylate cyclase 1, soluble, beta 2	-4.1
1385826_at	EST	-4.3
1393650_at	adiponutrin (predicted)	-4.4
1396434_at	EST	-4.5
1395330_at	EST	-4.5
1368627_at	regucalcin	-4.6
1384910_at	EST	-4.9
1397945_at	similar to WNT1 inducible signaling pathway protein 3 precursor (WISP-3) (UNQ462/PRO790)	-5.2
1369787_at	cholecystokinin A receptor	-5.4
1376243_at	similar to serine (or cysteine) proteinase inhibitor, clade B (ovalbumin), member 12	-5.6
1382239_at	similar to Myosin light chain kinase 2, skeletal/cardiac muscle (MLCK2) (predicted)	-6.4
1379411_at	similar to ENSANGP00000020885	-6.5
1384436_at	EST	-6.5
1387328_at	Cytochrome P450, subfamily IIC (mephenytoin 4-hydroxylase)	-6.6
1390596_at	melan-A (predicted)	-7.0
1398408_at	armadillo repeat containing 3 (predicted)	-7.3
1376789_at	similar to Myosin light chain kinase 2, skeletal/cardiac muscle (MLCK2) (predicted)	-7.9
1367977_at	synuclein, alpha	-9.0
1368435_at	cytochrome P450, family 8, subfamily b, polypeptide 1	-9.9
1370384_a_at	prolactin receptor	-70.2