Expression of PGC1α in glioblastoma multiforme patients

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Abstract. Peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) is a key modulator of mitochondrial biogenesis. It is a coactivator of multiple transcription factors and regulates metabolic processes. However, little is known about the expression and function of PGC1α in glioblastoma multiforme (GBM), the most prevalent and invasive type of brain tumor. The purpose of the present study was to investigate the biological function, localization and expression of PGC1α in GBM. It was observed that PGC1α expression is increased in the tumor cells, and a higher level of expression was observed in the mitochondria. Bioinformatics analyses identified that metabolic and mitochondrial genes were highly expressed in GBM cells, with a high PGC1α mRNA expression. Notably, mitochondrial function-associated genes were highly expressed in cells alongside high PGC1α expression. Collectively, the results of the present study indicate that PGC1α is associated with mitochondrial dysfunction in GBM and may have a role in tumor pathogenesis and progression.

Introduction

Peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) regulates metabolism (1,2), mitochondrial biogenesis and energy homeostasis (3,4). A number of studies have reported PGC1α as a central regulator of thermogenesis, mitochondrial biogenesis and adaptation to fasting in brown adipose tissue, skeletal muscle, cardiac muscle and the liver (1,5). By contrast, PGC1α in the central nervous system is less associated with energy state or thermogenesis (6). PGC1α expression in the central nervous system is high in the embryonic and early postnatal stages, but is decreased during maturation. PGC1α is expressed mostly by γ-aminobutyric acid-ergic neurons; however, a low level of PGC1α is also expressed in glia in the mature brain (7). There is a significant association between PGC1α and the metabolism of reactive oxygen species. PGC1α-null mice are considerably more sensitive to the neurodegenerative effects of the oxidative stressors 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and kainic acid, which suggests that PGC1α has a role in cellular antioxidant defense (8).

Numerous clinical studies have reported a significant association between PGC1α and a number of types of cancer. In breast, colon and ovarian cancer (9-12), a significant decrease in PGC1α expression accelerated the ‘Warburg effect’, which allows cancer cells to switch from mitochondrial to glycolytic metabolism to meet the metabolic requirements of proliferation (13). By contrast, increased PGC1α expression is present in melanoma, with a corresponding decrease in patient survival (14). The role of PGC1α in a number of cancer types remains unclear and warrants further studies.

Glioblastoma multiforme (GBM) is the most prevalent and invasive type of brain tumor. It aggressively infiltrates and spreads to the surrounding brain tissue via extensive microvascular proliferation. Numerous necrotic areas surrounded by palisading tumor cells are often observed (15). Although novel therapeutic strategies and improved clinical diagnostics have been introduced, GBM remains one of the most fatal diseases (16). An extensive amount of research has been...
performed to determine the mechanisms of unlimited proliferation in GBM, as well as its robust resistance to existing drugs and therapies (17,18) In the present study, the expression of PGC1α in normal cortical tissues and GBM tissues was compared. The results of the present study indicate that PGC1α may be a novel biomarker for GBM, as well as a novel target for future GBM therapy development.

Materials and methods

Patient samples. All experiments were performed in accordance with approved guidelines of Chungnam National University Hospital (CNUH; Daejeon, Republic of Korea). The Institutional Review Board of the CNUH approved the experimental protocols and all patients provided written informed consent prior to surgery. A total of 49 patients undergoing tumor resection surgeries at the Department of Neurosurgery, CNUH were enrolled, and pathologic diagnoses were confirmed by the Department of Pathology, CNUH via immunohistochemistry. First-time GBM diagnosis was used as the selection criterion, resulting in 26 patient samples that were included in the present study (Table I). The mean age of the patients was 58 years (range, 35 to 74 years). Normal brain tissue samples were obtained from cadavers or from autopsies of surrounding normal brain tissues of consenting GBM patients that underwent surgery (approval no. CNUH 2013-11-006).

Tissue microarray and immunostaining. Tissue microarrays (TMA) were used to perform the comparative histological analysis of normal brain and GBM tissues. The paraffin-embedded sample tissues were de-paraffinized and rehydrated in a graded alcohol series. Tissues were retrieved using 0.1 M citrate buffer (pH 6.0) and heated in a microwave vacuum histoprocessor (RHS-1; Milestone Medical, Bergamo, Italy) at a controlled temperature of 121°C for 15 min. Following washing with phosphate-buffered saline (pH 7.4), tissue sections were incubated with anti-PGC1α antibody (1:200; Santa Cruz Biotechnology, Inc., Dallas, TX, USA; #SC13067) overnight in a humidity chamber at 4°C. Immunohistochemical staining of the tissue sections was performed using avidin-biotin peroxidase complex as previously described (19,20). Additional TMA samples of normal cortex and GBM tissues were obtained from US Biomax, Inc. (Rockville, MD, USA).

All immunostaining was performed with antibodies that detected the N-terminal epitope of PGC1α (1:200; Santa Cruz Biotechnology, Inc.; #sc-13067). For immunofluorescence analysis, PGC1α and COX4 (1:200; Cell Signaling Technology, Inc., Danvers, MA, USA; #4D11B3-E8) were used as above but with either a Cy3-conjugated antibody (1:500; anti-rabbit; GE Healthcare Life Sciences Chalfont, UK; #PA43004) or a Cy2-conjugated secondary antibody (1:200; anti-mouse; GE Healthcare Life Sciences; #PA42002). Cell nuclei were visualized with DAPI, and double-stained sections were visualized using an Axioshot microscope (Carl Zeiss AG, Oberkochen, Germany).

Bioinformatics. The mRNA expression of 18,988 probes from 38 GBM cell lines was analyzed using the publicly available Broad-Novartis Cancer Cell Line Encyclopedia (CCLE) database (https://portals.broadinstitute.org/ccle/home) (21). The level of PGC1α mRNA expression among the 38 GBM cell lines was determined using CCLE. The mRNA expression data was normalized using the RankNormalize module in GenePattern (http://www.broadinstitute.org/cancer/software/genepattern). Gene Neighbors and Class Neighbors modules in GenePattern (http://www.broadinstitute.org/cancer/software/genepattern) were used to select genes that were closely associated with PGC1α (22). Hierarchical clustering was performed using complete linkage and Pearson rank-correlation distance with software provided by GenePattern (HierarchicalClustering; version 6). The colors in the heat-maps show the relative gene expression compared to the mean expression, with red being higher and blue lower. From the 18,988 gene set, 100 genes that were most correlated with PGC1α were selected for classification by Gene Ontology Enrichment Analysis (GO terms) using Database for Annotation, Visualization and Integrated Discovery (DAVID; http://david.abcc.ncifcrf.gov) (23). Differentially expressed genes (DEGs) were classified according to GO terms based on their biological process, molecular function or cellular component. DAVID provided an overview of extensive pathways (www.biocarta.com) in which various genes interacted, as well as the number of DEGs per pathway with a P-value representing gene enrichment. Gene enrichment score with P<0.05 represents a strong association rather than random chance (23). For genes with unknown biological processes, GeneMANIA database (http://www.genemania.org) was used to predict their function (24).

Statistical analysis. ImageJ software (version 1.47; National Institutes of Health, Bethesda, MD, USA) was used to quantify the optical density (pixels/mm²) or the intensity of images. The results from immunohistochemical staining were analyzed by a paired t-test between two groups. Data were presented as the mean ± standard error. Statistical analyses were performed using the Prism 5.0 software (GraphPad Prism Software, Inc., La Jolla, CA, USA). P<0.05 was considered to indicate a statistically significant difference. Data transformation (log conversion) selection and statistical analyses were performed with either the Microsoft Excel 11.0 (Microsoft Corporation, Redmond, WA, USA) or Prism 5.0 software.

Results

PGC1α is highly and variably expressed in GBM patients. To determine the association between PGC1α and GBM, levels of PGC1α protein in GBM and control (normal cortex) tissues were compared using publicly available TMAs from US Biomax, Inc. (Fig. 1). PGC1α was weakly detectable in the nuclei of cortical tissues in the control, whereas it was highly and sporadically expressed throughout the GBM tissues. Furthermore, PGC1α was mostly expressed within the cytoplasm with pale nucleic density (Fig. 1A). Bright-field immunohistochemical analysis of TMA images using a densitometer revealed that PGC1α expression varied between tumor samples (Fig. 1B).

For additional validation, PGC1α mRNA levels were determined in GBM cell lines (n=38) using the Broad-Novartis CCLE database (21). Comparative analysis of PGC1α
expression in GBM and five other types of cancer, including liver, ovarian, endometrial, breast and prostate carcinoma revealed that although there were variations in PGC1α mRNA expression between the GBM cell lines (Fig. 1D), the level of expression was increased in GBM compared to other cancer cell lines (Fig. 1C). Overall, these data demonstrate that PGC1α expression was increased in a subpopulation of GBM cells.

PGC1α is localized to the mitochondria in GBM. As a transcriptional coactivator, PGC1α is reported to be localized in the nuclei of the normal cortex (25). However, immunofluorescence analysis demonstrated localization of PGC1α in the perinuclear or cytoplasmic areas of GBM tissues (Fig. 2A). To confirm the subcellular localization of PGC1α, double staining with anti-PGC1α and anti-COX4 (a mitochondrial marker) antibodies was employed. There was a certain level of colocalization of PGC1α and COX4, thereby indicating that PGC1α was expressed in the mitochondria in GBM in addition to the perinuclear or cytoplasmic areas (Fig. 2B).

Gene Neighbors of PGC1α. Bioinformatics analysis of PGC1α-associated genes was performed. PGC1α mRNA expression levels detected in the GBM cell lines (n=38; Table II) ranged from 3.71 (log2) to 8.83 (log2), which corresponds to a fold-change of 2.38. A total of 100 genes that were strongly correlated with PGC1α were selected using Gene Neighbors (Fig. 3A) and classified using DAVID (23). Genes with significant differences (P<0.05) were classified into two groups based on GO terms: Biological process and cellular components (Tables III and IV). Genes highly expressed in GBM cell lines were largely associated with the generation of metabolite precursors and energy (e.g., the hexose or monosaccharide metabolic processes), oxidation reduction (e.g., mitochondrial electron transport, nicotinamide adenine dinucleotide to ubiquinone and the oxidoreduction coenzyme metabolic process), energy derivation by the oxidation of organic compounds [e.g., acetyl-CoA metabolic and catabolic processes, oxidative phosphorylation, tricarboxylic acid (TCA) cycle, aerobic respiration and glycolysis, and coenzyme metabolic and catabolic processes (e.g., cofactor catabolic process) (Fig. 3B). Notably, highly expressed genes were associated with the mitochondria (e.g., mitochondrial membrane, mitochondrial matrix and mitochondrial respiratory chain), organelle membranes (e.g., organelle inner membrane) and the cellular envelope (Fig. 3C). This observation is in agreement
with the finding that PGC1α is localized in the mitochondria in GBM as previously described.

**PGC1α expression is highly correlated with mitochondrial function in GBM.** Two-way hierarchical clustering of targeted gene sets was performed between five GBM cell lines with the highest (LNZ308, LN464, DBTRG05MG, LN235 and SNU626) and lowest levels (LN229, KNS60, SF172, SNU466 and KS1) of PGC1α expression. The expression of TCA cycle- (P<0.0001),

| GBM cell lines | PGC1α mRNA |
|---------------|------------|
| LNZ308        | 8.83       |
| LN464         | 8.79       |
| DBTRG05MG     | 8.65       |
| LN235         | 8.40       |
| SNU626        | 7.65       |
| GB1           | 7.45       |
| YKG1          | 6.64       |
| U343          | 6.59       |
| LN428         | 6.52       |
| SNB19         | 6.49       |
| GMS10         | 6.27       |
| LN340         | 6.17       |
| KNS81         | 6.11       |
| 8MGBA         | 5.72       |
| SNU201        | 5.63       |
| T98G          | 5.53       |
| YH13          | 5.33       |
| LN382         | 5.19       |
| CAS1          | 5.11       |
| U178          | 4.71       |
| SF295         | 4.69       |
| SNU1105       | 4.62       |
| SNU489        | 4.60       |
| DKMG          | 4.42       |
| BECKER        | 4.30       |
| 42MGBA        | 4.29       |
| KG1C          | 4.22       |
| A172          | 4.17       |
| LN443         | 4.13       |
| LN215         | 4.09       |
| AM38          | 4.04       |
| LN18          | 4.04       |
| M059K         | 4.02       |
| LN229         | 4.00       |
| KNS60         | 4.00       |
| SF172         | 3.84       |
| SNU466        | 3.74       |
| KS1           | 3.71       |

GBM, glioblastoma multiforme; PGC1α, proliferator-activated receptor γ coactivator 1α.
Table III. List of Gene Neighbors of peroxisome proliferator-activated receptor γ coactivator 1α differentially expressed in glioblastoma multiforme cells.

| Gene symbol | Description |
|-------------|-------------|
| **Generation of precursor metabolites and energy** |
| ATP5J       | ATP synthase, H+ transporting, mitochondrial Fo complex, subunit F6 |
| ATP5B       | ATP synthase, H+ transporting, mitochondrial F1 complex, β-polypeptide |
| NDUFA1      | NADH dehydrogenase (ubiquinone) 1α subcomplex, 1, 7.5 kDa |
| NDUFA4      | NADH dehydrogenase (ubiquinone) 1α subcomplex, 4, 9 kDa |
| NDUFA7      | NADH dehydrogenase (ubiquinone) 1α subcomplex, 7, 14.5 kDa |
| ACO2        | Aconitase 2, mitochondrial |
| GYG2        | Glycogenin 2 |
| IDH3A       | Isocitrate dehydrogenase 3 (NAD+) α |
| MDH1        | Malate dehydrogenase 1, NAD (soluble) |
| MCHR1       | Melanin-concentrating hormone receptor 1 |
| OGDHL       | Oxoglutarate dehydrogenase-like |
| PDHA1       | Pyruvate dehydrogenase (lipoamide) α 1 |
| **Oxidation reduction** |
| NDUFA1      | NADH dehydrogenase (ubiquinone) 1α subcomplex, 1, 7.5 kDa |
| NDUFA4      | NADH dehydrogenase (ubiquinone) 1α subcomplex, 4, 9 kDa |
| NDUFA7      | NADH dehydrogenase (ubiquinone) 1α subcomplex, 7, 14.5 kDa |
| AIFM1       | Apoptosis-inducing factor, mitochondrion-associated, 1 |
| CYP27A1     | Cytochrome p450, family 27, subfamily A, polypeptide 1 |
| COX5A       | Cytochrome c oxidase subunit Va |
| HCCS        | Holocytochrome c synthase |
| IDH3A       | Isocitrate dehydrogenase 3 (NAD+) α |
| MDH1        | Malate dehydrogenase 1, NAD (soluble) |
| OGDHL       | Oxoglutarate dehydrogenase-like |
| PIPOX       | Pyroglutarate dehydrogenase-like |
| PRODH       | Prolactin dehydrogenase (oxidase) 1 |
| PDHA1       | Pyruvate dehydrogenase (lipoamide) α 1 |
| **Energy derivation by oxidation of organic compounds** |
| NDUFA1      | NADH dehydrogenase (ubiquinone) 1α subcomplex, 1, 7.5 kDa |
| NDUFA4      | NADH dehydrogenase (ubiquinone) 1α subcomplex, 4, 9 kDa |
| NDUFA7      | NADH dehydrogenase (ubiquinone) 1α subcomplex, 7, 14.5 kDa |
| ACO2        | Aconitase 2, mitochondrial |
| GYG2        | Glycogenin 2 |
| IDH3A       | Isocitrate dehydrogenase 3 (NAD+) α |
| MDH1        | Malate dehydrogenase 1, NAD (soluble) |
| **Cellular respiration** |
| NDUFA1      | NADH dehydrogenase (ubiquinone) 1α subcomplex, 1, 7.5 kDa |
| NDUFA4      | NADH dehydrogenase (ubiquinone) 1α subcomplex, 4, 9 kDa |
| NDUFA7      | NADH dehydrogenase (ubiquinone) 1α subcomplex, 7, 14.5 kDa |
| ACO2        | Aconitase 2, mitochondrial |
| IDH3A       | Isocitrate dehydrogenase 3 (NAD+) α |
| MDH1        | Malate dehydrogenase 1, NAD (soluble) |
| **Acetyl-CoA metabolic process** |
| ACO2        | Aconitase 2, mitochondrial |
| ACS1        | Acyl-CoA synthetase short-chain family member 1 |
| IDH3A       | Isocitrate dehydrogenase 3 (NAD+) α |
| MDH1        | Malate dehydrogenase 1, NAD (soluble) |
| **Coenzyme metabolic process** |
| ACO2        | Aconitase 2, mitochondrial |
| ACS1        | Acyl-CoA synthetase short-chain family member 1 |
Table III. Continued.

| Gene symbol | Description |
|-------------|-------------|
| IDH3A       | Isocitrate dehydrogenase 3 (NAD⁺) α |
| MDH1        | Malate dehydrogenase 1, NAD (soluble) |

**Oxidation phosphorylation**

| Gene symbol | Description |
|-------------|-------------|
| ATP5J       | ATP synthase, H⁺ transporting, mitochondrial Fo complex, subunit F6 |
| ATP5B       | ATP synthase, H⁺ transporting, mitochondrial F1 complex, β polypeptide |
| NDUFA1      | NADH dehydrogenase (ubiquinone) 1 α subcomplex, 1, 7.5 kDa |
| NDUFA4      | NADH dehydrogenase (ubiquinone) 1 α subcomplex, 4, 9 kDa |
| NDUFA7      | NADH dehydrogenase (ubiquinone) 1 α subcomplex, 7, 14.5 kDa |

**Cofactor metabolic process**

| Gene symbol | Description |
|-------------|-------------|
| ACO2        | Aconitase 2, mitochondrial |
| ACS51       | Acyl-CoA synthetase short-chain family member 1 |
| COQ9        | Coenzyme Q9 homolog (S. cerevisiae) |
| IDH3A       | Isocitrate dehydrogenase 3 (NAD⁺) α |
| MDH1        | Malate dehydrogenase 1, NAD (soluble) |
| PIP0X       | Pipecolic acid oxidase |

**Acetyl-CoA catabolic process**

| Gene symbol | Description |
|-------------|-------------|
| ACO2        | Aconitase 2, mitochondrial |
| IDH3A       | Isocitrate dehydrogenase 3 (NAD⁺) α |
| MDH1        | Malate dehydrogenase 1, NAD (soluble) |

**Tricarboxylic acid cycle**

| Gene symbol | Description |
|-------------|-------------|
| ACO2        | Aconitase 2, mitochondrial |
| IDH3A       | Isocitrate dehydrogenase 3 (NAD⁺) α |
| MDH1        | Malate dehydrogenase 1, NAD (soluble) |

**Coenzyme catabolic process**

| Gene symbol | Description |
|-------------|-------------|
| ACO2        | Aconitase 2, mitochondrial |
| IDH3A       | Isocitrate dehydrogenase 3 (NAD⁺) α |
| MDH1        | Malate dehydrogenase 1, NAD (soluble) |

**Cofactor catabolic process**

| Gene symbol | Description |
|-------------|-------------|
| ACO2        | Aconitase 2, mitochondrial |
| IDH3A       | Isocitrate dehydrogenase 3 (NAD⁺) α |
| MDH1        | Malate dehydrogenase 1, NAD (soluble) |

**Aerobic respiration**

| Gene symbol | Description |
|-------------|-------------|
| ACO2        | Aconitase 2, mitochondrial |
| IDH3A       | Isocitrate dehydrogenase 3 (NAD⁺) α |
| MDH1        | Malate dehydrogenase 1, NAD (soluble) |

**Hexose metabolic process**

| Gene symbol | Description |
|-------------|-------------|
| PFKFB3      | 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 |
| GYG2        | Glycogenin 2 |
| MDH1        | Malate dehydrogenase 1, NAD (soluble) |
| OGDHL       | Oxoglutarate dehydrogenase-like |
| PDHA1       | Pyruvate dehydrogenase (lipoamide) α 1 |

**Mitochondrial electron transport, NADH to ubiquinone**

| Gene symbol | Description |
|-------------|-------------|
| NDUFA1      | NADH dehydrogenase (ubiquinone) 1 α subcomplex, 1, 7.5 kDa |
| NDUFA4      | NADH dehydrogenase (ubiquinone) 1 α subcomplex, 4, 9 kDa |
| NDUFA7      | NADH dehydrogenase (ubiquinone) 1 α subcomplex, 7, 14.5 kDa |

**Glycolysis**

| Gene symbol | Description |
|-------------|-------------|
| MDH1        | Malate dehydrogenase 1, NAD (soluble) |
| OGDHL       | Oxoglutarate dehydrogenase-like |
| PDHA1       | Pyruvate dehydrogenase (lipoamide) α 1 |
Table III. Continued.

| Gene symbol | Description |
|-------------|-------------|
| **Monosaccharide metabolic process** | |
| PFKFB3 | 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 |
| GYG2 | Glycogenin 2 |
| MDH1 | Malate dehydrogenase 1, NAD (soluble) |
| OGDHL | Oxoglutarate dehydrogenase-like |
| PDHA1 | Pyruvate dehydrogenase (lipoamide) α 1 |
| **Oxidoreduction coenzyme metabolic process** | |
| COQ9 | Coenzyme Q9 homolog (S. cerevisiae) |
| IDH3A | Isocitrate dehydrogenase 3 (NAD⁺) α |
| MDH1 | Malate dehydrogenase 1, NAD (soluble) |
| **Unknown biological process** | |
| CEND1 | Cell cycle exit and neuronal differentiation 1 |
| COX7B | Cytochrome c oxidase subunit VIIIb |
| TMCC2 | Transmembrane and coiled-coil domain family 2 |
| SOX13 | SRY (sex determining region Y)-box 13 |
| BTBD3 | BTB (POZ) domain containing 3 |
| ZNF222 | Zinc finger protein 222 |
| DCUN1D2 | DCN1, defective in cullin neddylation 1, domain containing 2 |
| MFSD2A | Major facilitator superfamily domain containing 2A |
| CX3CL1 | Chemokine (C-X3-C motif) ligand 1 |
| GSTM4 | Glutathione S-transferase mu 4 |
| PIGA | Phosphatidylinositol glycan anchor biosynthesis, class A |
| ITPKB | Inositol-trisphosphate 3-kinase B |
| TSPAN16 | Tetraspanin 16 |
| CHCHD3 | Coiled-coil-helix-coiled-coil-helix domain containing 3 |
| APOO | Apolipoprotein O |
| AKAP11 | A kinase (PRKA) anchor protein 11 |
| NEBL | Nebulette |
| SCUBE3 | Signal peptide, CUB domain, EGF-like 3 |
| RRAGD | Ras-related GTP binding D |
| IGHV1-2 | Immunoglobulin heavy variable 1-2 |
| RRAGD | Ras-related GTP binding D |
| TRIM2 | Tripartite motif containing 2 |
| TLE6 | Transducin-like enhancer of split 6 (E(sp1) homolog, Drosophila) |
| LINC00461 | Long intergenic non-protein coding RNA 461 |
| SLC25A25 | Solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 25 |
| SLC25A11 | Solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 11 |
| IVNS1ABP | Influenza virus NS1A binding protein |
| HEY1 | Hairy/enhancer-of-split related with YRPW motif 1 |
| NDRG2 | NDRG family member 2 |
| COX5B | Cytochrome c oxidase subunit Vb |
| MRPL34 | Mitochondrial ribosomal protein L34 |
| STK32A | Serine/threonine kinase 32A |
| MEGF8 | Multiple EGF-like-domains 8 |
| ATP1A1 | ATPase, Na⁺/K⁺ transporting, α 1 polypeptide |
| RBPMS2 | RNA binding protein with multiple splicing 2 |
| LPL | Lipoprotein lipase |
| FURIN | Furin (paired basic amino acid cleaving enzyme) |
| ASAH1 | N-aclysphingosine amidohydrolase (acid ceramidase) 1 |
| KHLH15 | Kelch-like family member 15 |
| BTBD1 | BTB (POZ) domain containing 1 |
| PTCDD3 | Pentatricopeptide repeat domain 3 |
oxidative phosphorylation (OXPHOS) (P<0.0001) and lipogenesis-associated genes (P<0.01) was significantly increased in the PGC1α-upregulated cells compared with the PGC1α-downregulated cells (Fig. 4A-C). Furthermore, the expression of antioxidant-associated genes was significantly increased in the PGC1α-upregulated cell lines compared with the PGC1α-downregulated cell lines (Fig. 4D; P<0.0001). Taken together, the data in Figs. 3 and 4 suggest that metabolic and mitochondrial genes were highly expressed in parallel with PGC1α. Notably, genes associated with mitochondrial functions, including TCA cycle, OXPHOS, lipogenesis and antioxidant genes, were highly expressed in cells with high PGC1α levels (Fig. 4), which corroborates the results from a recent study (26) and the colocalization data as previously described in the present study.

Class Neighbors of PGC1α up- and downregulated GBM cell lines. Bioinformatics analysis using Class Neighbors yielded two classes of GBM cell lines. Class A contained the ten most PGC1α-upregulated GBM cell lines, and class B contained the ten most PGC1α-downregulated GBM cell lines (Fig. 5A). Out of a total of 18,988 probe sets, 100 genes that were most strongly correlated with classes A and B and most highly expressed were selected. DAVID analysis classified these genes into three groups based on GO terms: i) Biological process, ii) molecular function and iii) cellular components (Fig. 5B and C; Table III. Continued.

| Gene symbol | Description |
|-------------|-------------|
| RBM38 | RNA binding motif protein 38 |
| LYNX1 | Ly/6/neurotoxin 1 |
| EFHA1 | Mitochondrial calcium uptake 2 |
| NCOA1 | Nuclear receptor coactivator 1 |
| KIF13B | Kinesin family member 13B |
| FAM199X | Family with sequence similarity 199, X-linked |
| PRPM | Reprimo, TP53 dependent G2 arrest mediator candidate |
| ZNF462 | Zinc finger protein 462 |
| ANXAI3 | Annexin A13 |
| SPG20OS | SPG20 opposite strand |
| GPR98 | G protein-coupled receptor 98 |
| GK | Glycerol kinase |
| UCK1 | Uridine-cytidine kinase 1 |
| LNX2 | Ligand of numb-protein X2 |
| SPG20 | Spastic paraplegia 20 (Troyer syndrome) |
| WNK3 | WNK lysine deficient protein kinase 3 |
| LOC100506108 | LOC100506108 |
| GCNT2 | Glucosaminyl (N-acetyl) transferase 2, I-branching enzyme (I blood group) |
| SLC31A1 | Solute carrier family 31 (copper transporter), member 1 |
| OSTM1 | Osteopetrosis associated transmembrane protein 1 |
| TMF1 | TATA element modulatory factor 1 |
| TSPAN3 | Tetraspanin 3 |
| COL4A3 | Collagen, type IV, α3 (Goodpasture antigen) |
| GPMB6 | Glycoprotein M6B |
| PELI2 | Pellino E3 ubiquitin protein ligase family member 2 |
| LOC401431 | LOC401431 |
| UBAC1 | UBA domain containing 1 |
| ATG4D | Autophagy related 4D, cysteine peptidase |
| COMMD6 | COMM domain containing 6 |
| FAM65B | Family with sequence similarity 65, member B |
| TMEM2 | Transmembrane protein 2 |
| ASB9 | Ankyrin repeat and SOCS box containing 9 |
| BCAM | Basal cell adhesion molecule (Lutheran blood group) |
| KIF16B | Kinesin family member 16B |
| CHKA | Choline kinase α |
| PPM1E | Protein phosphatase, Mg2+/Mn2+ dependent, 1E |
| CA2 | Carbonic anhydrase II |
Tables V–VIII). GeneMANIA database analysis resulted in the identification of 52 genes with previously unknown biological interactions with PGC1α, including necdin (NDN).

In addition, when genes were analyzed according to cell signaling pathway (BioCarta database), 3 signaling pathways in class A and 5 in class B were identified as statistically significant (P<0.05; Table IX). The results of the present study demonstrate that class A genes play roles in signaling pathways associated with metabolic and mitochondrial electron transport and that class B genes are involved in signaling pathways associated with differentiation and immune function.

**Discussion**

The objective of the present study was to investigate the association between aberrant expression of PGC1α and GBM, and
the role PGC1α may have in patient survival. Protein level data demonstrated that PGC1α expression was increased in a subpopulation of tumor cells, although there were variations between different GBM cell lines and patients. PGC1α localization was identified to differ between GBM tissues and the normal cortex (Fig. 2). These results corroborated...
Table V. List of class A genes highly expressed in peroxisome proliferator-activated receptor γ coactivator 1α-upregulated glioblastoma multiforme cells.

| Gene          | Description                        | Score | P-value       | Fold-change | Up mean | Down mean |
|---------------|------------------------------------|-------|---------------|-------------|---------|-----------|
| **Developmental processes** |                                   |       |               |             |         |           |
| CLEC2B        | C-type lectin domain family 2, member B | 2.63  | 3.2x10^3      | 1.44        | 5.88    | 4.09      |
| EFHD1         | EF-hand domain family, member D1   | 2.22  | 4.4x10^2      | 1.31        | 6.03    | 4.61      |
| EPHA3         | EPH receptor A3                    | 2.45  | 1.9x10^2      | 1.39        | 5.33    | 3.83      |
| HHIL2         | HHIP-like 2                        | 3.52  | 2.6x10^3      | 1.21        | 5.49    | 4.53      |
| MAMDC2        | MAM domain containing 2            | 2.49  | 2.2x10^2      | 1.42        | 6.76    | 4.77      |
| POU3F2        | POU class 3 homeobox 2             | 2.54  | 2.6x10^3      | 1.40        | 7.20    | 5.15      |
| BHLHE41       | Basic helix-loop-helix family, member e41 | 2.92  | 6.2x10^3      | 1.26        | 6.14    | 4.89      |
| CDH6          | Cadherin 6, type 2, K-cadherin (fetal kidney) | 2.80  | 1.1x10^3      | 1.35        | 5.83    | 4.31      |
| CELSR2        | Cadherin, EGF LAG seven-pass G-type receptor 2 | 2.80  | 1.2x10^4      | 1.21        | 7.78    | 6.42      |
| CXCR4         | Chemokine (C-X-C motif) receptor 4 | 2.55  | 1.5x10^3      | 1.44        | 6.04    | 4.20      |
| CNHI3         | Cornichon family AMPA receptor auxiliary protein 3 | 2.41  | 3.3x10^2      | 1.41        | 7.22    | 5.11      |
| CCNA1         | Cyclin A1                          | 2.56  | 1.1x10^3      | 1.32        | 5.71    | 4.32      |
| FABP7         | Fatty acid binding protein 7, brain | 2.26  | 3.1x10^2      | 1.57        | 6.87    | 4.38      |
| FBLN1         | Fibulin 1                          | 2.62  | 1.9x10^2      | 1.27        | 7.35    | 5.78      |
| FOXA2         | Forkhead box A2                    | 2.18  | 6.2x10^2      | 1.36        | 5.56    | 4.09      |
| GPM6B         | Glycoprotein M6B                   | 2.14  | 4.8x10^2      | 1.46        | 7.60    | 5.19      |
| HES1          | Hairy and enhancer of split 1, (Drosophila) | 3.29  | 4.2x10^3      | 1.21        | 8.42    | 6.98      |
| HEY1          | Hairy/enhancer-of-split related with YRPW motif 1 | 2.49  | 2.3x10^2      | 1.28        | 8.16    | 6.39      |
| IRX1          | Iroquois homeobox 1                | 2.81  | 8.4x10^3      | 1.48        | 6.61    | 4.47      |
| JAG1          | Jagged 1                           | 3.16  | 6.0x10^3      | 1.22        | 7.89    | 6.48      |
| MYL5          | Myosin, light chain 5, regulatory  | 3.19  | 5.6x10^3      | 1.25        | 6.73    | 5.40      |
| NRG2          | Neuregulin 2                       | 2.73  | 1.4x10^2      | 1.22        | 4.99    | 4.09      |
| NRP2          | Neuropilin 2                       | 2.75  | 1.2x10^2      | 1.25        | 6.74    | 5.40      |
| PTHLH         | Parathyroid hormone-like hormone    | 2.46  | 1.9x10^2      | 1.42        | 6.77    | 4.75      |
| PRICKLE2      | Prickle homolog 2 (Drosophila)     | 2.46  | 2.3x10^2      | 1.22        | 8.15    | 6.70      |
| SALL1         | Sal-like 1 (Drosophila)            | 2.41  | 2.5x10^2      | 1.36        | 6.83    | 5.04      |
| SCUBE3        | Signal peptide, CUB domain, EGF-like 3 | 2.63  | 3.6x10^3      | 1.34        | 7.76    | 5.78      |
| TLR4          | Toll-like receptor 4               | 2.82  | 9.8x10^3      | 1.36        | 6.29    | 4.61      |
| **Signal transduction** |                                    |       |               |             |         |           |
| EPHA3         | EPH receptor A3                    | 2.45  | 1.9x10^2      | 1.39        | 5.33    | 3.83      |
| GPR56         | G protein-coupled receptor 56      | 3.00  | 9.4x10^3      | 1.26        | 7.68    | 6.07      |
| PDZRN3        | PDZ domain containing ring finger 3 | 2.61  | 1.5x10^2      | 1.39        | 8.00    | 5.75      |
| RASSF2        | Ras association (RalGDS/AF-6) domain 2 family member | 3.25  | 1.0x10^1      | 1.50        | 6.64    | 4.44      |
| WNK3          | WNK lysine deficient protein kinase 3 | 3.06  | 5.4x10^3      | 1.21        | 5.25    | 4.36      |
| CDH6          | Cadherin 6, type 2, K-cadherin (fetal kidney) | 2.80  | 1.1x10^2      | 1.35        | 5.83    | 4.31      |
| CELSR2        | Cadherin, EGF LAG seven-pass G-type receptor 2 | 2.80  | 1.2x10^2      | 1.21        | 7.78    | 6.42      |
| CXCR4         | Chemokine (C-X-C motif) receptor 4 | 2.55  | 1.5x10^2      | 1.44        | 6.04    | 4.20      |
| CX3CL1        | Chemokine (C-X3-C motif) ligand 1  | 4.01  | 8.0x10^4      | 1.26        | 5.89    | 4.67      |
| CNHI3         | Cornichon family AMPA receptor auxiliary protein 3 | 2.41  | 3.3x10^2      | 1.41        | 7.22    | 5.11      |
| FABP7         | Fatty acid binding protein 7, brain | 2.26  | 3.1x10^2      | 1.57        | 6.87    | 4.38      |
| FBLN1         | Fibulin 1                          | 2.62  | 1.9x10^2      | 1.27        | 7.35    | 5.78      |
| FOXA2         | Forkhead box A2                    | 2.18  | 6.2x10^2      | 1.36        | 5.56    | 4.09      |
| ITPR1         | Inositol 1,4,5-trisphosphate receptor, type 1 | 2.68  | 1.4x10^2      | 1.25        | 6.99    | 5.60      |
| ITPKB         | Inositol-trisphosphate 3-kinase B  | 2.60  | 1.9x10^2      | 1.20        | 6.69    | 5.58      |
| NRG2          | Neuregulin 2                       | 2.73  | 1.4x10^2      | 1.22        | 4.99    | 4.09      |
| NPY1R         | Neuropeptide Y receptor Y1         | 2.00  | 5.5x10^2      | 1.41        | 7.53    | 4.08      |
| NRP2          | Neuropilin 2                       | 2.75  | 1.2x10^2      | 1.25        | 6.74    | 5.40      |
Table V. Continued.

| Gene   | Description                                      | Score | P-value | Fold-change | Up\(^{\text{a}}\) mean | Down\(^{\text{a}}\) mean |
|--------|--------------------------------------------------|-------|---------|-------------|-------------------------|-------------------------|
| PDE4B  | Phosphodiesterase 4B, cAMP-specific              | 2.59  | 2.1x10\(^2\) | 1.26        | 6.83                    | 5.42                    |
| PDGFRL | Platelet-derived growth factor receptor-like     | 2.55  | 2.5x10\(^2\) | 1.29        | 6.76                    | 5.22                    |
| SFRP1  | Secreted frizzled-related protein 1              | 2.33  | 3.5x10\(^2\) | 1.42        | 7.77                    | 5.46                    |
| SCG2   | Secretogranin II                                 | 2.50  | 2.0x10\(^2\) | 1.43        | 8.08                    | 5.64                    |
| SCUBE3 | Signal peptide, CUB domain, EGF-like 3          | 2.63  | 3.6x10\(^3\) | 1.34        | 7.76                    | 5.78                    |
| TLR4   | Toll-like receptor 4                             | 2.82  | 9.8x10\(^3\) | 1.36        | 6.29                    | 4.61                    |
| TMTC1  | Transmembrane and tetratricopeptide repeat      | 2.43  | 2.5x10\(^2\) | 1.29        | 6.10                    | 4.72                    |

**Ectoderm development**

| Gene   | Description                                      | Score | P-value | Fold-change | Up\(^{\text{a}}\) mean | Down\(^{\text{a}}\) mean |
|--------|--------------------------------------------------|-------|---------|-------------|-------------------------|-------------------------|
| EPRA3  | EPH receptor A3                                   | 2.45  | 1.9x10\(^2\) | 1.39        | 5.33                    | 3.83                    |
| CDH6   | Cadherin 6, type 2, K-cadherin (fetal kidney)    | 2.80  | 1.1x10\(^2\) | 1.35        | 5.83                    | 4.31                    |
| CELSR2 | Cadherin, EGF LAG seven-pass G-type receptor 2   | 2.80  | 1.2x10\(^2\) | 1.21        | 7.78                    | 6.42                    |
| CXCR4  | Chemokine (C-X-C motif) receptor 4               | 2.55  | 1.5x10\(^2\) | 1.44        | 6.04                    | 4.20                    |
| FABP7  | Fatty acid binding protein 7, brain              | 2.26  | 3.1x10\(^3\) | 1.57        | 6.87                    | 4.38                    |
| FOXA2  | Forkhead box A2                                  | 2.18  | 6.2x10\(^2\) | 1.36        | 5.56                    | 4.09                    |
| GPM6B  | Glycoprotein M6B                                  | 2.14  | 4.8x10\(^2\) | 1.46        | 7.60                    | 5.19                    |
| HES1   | Hairy and enhancer of split 1, (*Drosophila*)    | 3.29  | 4.2x10\(^3\) | 1.21        | 8.42                    | 6.98                    |
| HEY1   | Hairy/enhancer-of-split related with YRPW motif 1| 2.49  | 2.3x10\(^3\) | 1.28        | 8.16                    | 6.39                    |
| IRX1   | Iroquois homeobox 1                              | 2.81  | 8.4x10\(^3\) | 1.48        | 6.61                    | 4.47                    |
| JAG1   | Jagged 1                                         | 3.16  | 6.6x10\(^3\) | 1.22        | 7.99                    | 6.48                    |
| NRG2   | Neuregulin 2                                     | 2.73  | 1.4x10\(^3\) | 1.22        | 4.99                    | 4.09                    |
| NRP2   | Neuregin 2                                       | 2.75  | 1.2x10\(^3\) | 1.25        | 6.74                    | 5.40                    |

**Cell structure and motility**

| Gene   | Description                                      | Score | P-value | Fold-change | Up\(^{\text{a}}\) mean | Down\(^{\text{a}}\) mean |
|--------|--------------------------------------------------|-------|---------|-------------|-------------------------|-------------------------|
| CELSR2 | Cadherin, EGF LAG seven-pass G-type receptor 2   | 2.80  | 1.2x10\(^2\) | 1.21        | 7.78                    | 6.42                    |
| CXCR4  | Chemokine (C-X-C motif) receptor 4               | 2.55  | 1.5x10\(^2\) | 1.44        | 6.04                    | 4.20                    |
| COL7A1 | Collagen, type VII, α 1                           | 2.53  | 2.0x10\(^2\) | 1.26        | 8.29                    | 6.58                    |
| DCLK1  | Doublecortin-like kinase 1                       | 2.69  | 1.6x10\(^2\) | 1.21        | 4.91                    | 4.06                    |
| DNM3   | Dynamin 3                                        | 2.22  | 3.7x10\(^2\) | 1.21        | 6.13                    | 5.06                    |
| DYNCI11| Dynclin, cytoplasmic 1, intermediate chain 1     | 2.85  | 1.1x10\(^3\) | 1.42        | 7.89                    | 5.55                    |
| FOXA2  | Forkhead box A2                                  | 2.18  | 6.2x10\(^2\) | 1.36        | 5.56                    | 4.09                    |
| GPM6B  | Glycoprotein M6B                                  | 2.14  | 4.8x10\(^2\) | 1.46        | 7.60                    | 5.19                    |
| ITPR1  | Inositol 1,4,5-trisphosphate receptor, type 1    | 2.68  | 1.4x10\(^2\) | 1.25        | 6.99                    | 5.60                    |
| JAG1   | Jagged 1                                         | 3.16  | 6.0x10\(^3\) | 1.22        | 7.89                    | 6.48                    |
| MYL5   | Myosin, light chain 5, regulatory                | 3.19  | 5.6x10\(^3\) | 1.25        | 6.73                    | 5.40                    |
| PRICKLE2| Prickle homolog 2 (*Drosophila*)                 | 2.46  | 2.3x10\(^3\) | 1.22        | 8.15                    | 6.70                    |
| SPP1   | Secreted phosphoprotein 1                        | 0.82  | 4.2x10\(^1\) | 1.03        | 7.03                    | 7.22                    |

**Neurogenesis**

| Gene   | Description                                      | Score | P-value | Fold-change | Up\(^{\text{a}}\) mean | Down\(^{\text{a}}\) mean |
|--------|--------------------------------------------------|-------|---------|-------------|-------------------------|-------------------------|
| EPRA3  | EPH receptor A3                                   | 2.45  | 1.9x10\(^2\) | 1.39        | 5.33                    | 3.83                    |
| CDH6   | Cadherin 6, type 2, K-cadherin (fetal kidney)    | 2.80  | 1.1x10\(^2\) | 1.35        | 5.83                    | 4.31                    |
| CELSR2 | Cadherin, EGF LAG seven-pass G-type receptor 2   | 2.80  | 1.2x10\(^2\) | 1.21        | 7.78                    | 6.42                    |
| CXCR4  | Chemokine (C-X-C motif) receptor 4               | 2.55  | 1.5x10\(^2\) | 1.44        | 6.04                    | 4.20                    |
| FOXA2  | Forkhead box A2                                  | 2.18  | 6.2x10\(^2\) | 1.36        | 5.56                    | 4.09                    |
| GPM6B  | Glycoprotein M6B                                  | 2.14  | 4.8x10\(^2\) | 1.46        | 7.60                    | 5.19                    |
| HES1   | Hairy and enhancer of split 1, (*Drosophila*)    | 3.29  | 4.2x10\(^3\) | 1.21        | 8.42                    | 6.98                    |
| HEY1   | Hairy/enhancer-of-split related with YRPW motif 1| 2.49  | 2.3x10\(^3\) | 1.28        | 8.16                    | 6.39                    |
| IRX1   | Iroquois homeobox 1                              | 2.81  | 8.4x10\(^3\) | 1.48        | 6.61                    | 4.47                    |
| JAG1   | Jagged 1                                         | 3.16  | 6.0x10\(^3\) | 1.22        | 7.99                    | 6.48                    |
| NRG2   | Neuregulin 2                                     | 2.73  | 1.4x10\(^3\) | 1.22        | 4.99                    | 4.09                    |
| NRP2   | Neuregin 2                                       | 2.75  | 1.2x10\(^3\) | 1.25        | 6.74                    | 5.40                    |
| Gene       | Description                                                                 | Score | P-value | Fold-change | Up^a mean | Down^a mean |
|-----------|------------------------------------------------------------------------------|-------|---------|-------------|-----------|-------------|
| **Cell communication**                                                                                                           |
| **CDH6**  | Cadherin 6, type 2, K-cadherin (fetal kidney)                                | 2.80  | 1.1x10^2 | 1.35        | 5.83      | 4.31        |
| **CELSR2**| Cadherin, EGF LAG seven-pass G-type receptor 2                               | 2.80  | 1.2x10^2 | 1.21        | 7.78      | 6.42        |
| **FABP7** | Fatty acid binding protein 7, brain                                          | 2.26  | 3.1x10^3 | 1.57        | 6.87      | 4.38        |
| **FLNB1** | Fibulin 1                                                                     | 2.62  | 1.9x10^3 | 1.27        | 7.35      | 5.78        |
| **FOXO2** | Forkhead box A2                                                               | 2.18  | 6.2x10^2 | 1.36        | 5.56      | 4.09        |
| **ITPR1** | Inositol 1,4,5-trisphosphate receptor, type 1                                 | 2.68  | 1.4x10^3 | 1.25        | 6.99      | 5.60        |
| **NRG2**  | Neuregulin 2                                                                  | 2.73  | 1.4x10^3 | 1.22        | 4.99      | 4.09        |
| **SFRP1** | Secreted frizzled-related protein 1                                           | 2.33  | 3.5x10^3 | 1.42        | 7.77      | 5.46        |
| **SCG2**  | Secretogranin II                                                             | 2.50  | 2.0x10^2 | 1.43        | 8.08      | 5.64        |
| **SCUBE3**| Signal peptide, CUB domain, EGF-like 3                                        | 2.63  | 3.6x10^3 | 1.34        | 7.76      | 5.78        |
| **TMTC1** | Transmembrane and tetratricopeptide repeat containing 1                      | 2.43  | 2.5x10^2 | 1.29        | 6.10      | 4.72        |
| **Mesoderm development**                                                             |                                     |       |          |             |           |             |
| **EFHD1** | EF-hand domain family, member D1                                              | 2.22  | 4.4x10^2 | 1.31        | 6.03      | 4.61        |
| **EPHA3** | EPH receptor A3                                                               | 2.45  | 1.9x10^3 | 1.39        | 5.33      | 3.83        |
| **FLNB1** | Fibulin 1                                                                     | 2.62  | 1.9x10^3 | 1.27        | 7.35      | 5.78        |
| **FOXO2** | Forkhead box A2                                                               | 2.18  | 6.2x10^2 | 1.36        | 5.56      | 4.09        |
| **MYL5**  | Myosin, light chain 5, regulatory                                             | 3.19  | 5.6x10^3 | 1.25        | 6.73      | 5.40        |
| **NRP2**  | Neuropilin 2                                                                  | 2.75  | 1.2x10^2 | 1.25        | 6.74      | 5.40        |
| **PTHHL** | Parathyroid hormone-like hormone                                              | 2.46  | 1.9x10^3 | 1.42        | 6.77      | 4.75        |
| **SCUBE3**| Signal peptide, CUB domain, EGF-like 3                                        | 2.63  | 3.6x10^3 | 1.34        | 7.76      | 5.78        |
| **Cell structure**                                                                  |                                     |       |          |             |           |             |
| **CELSR2**| Cadherin, EGF LAG seven-pass G-type receptor 2                               | 2.80  | 1.2x10^2 | 1.21        | 7.78      | 6.42        |
| **COL7A1**| Collagen, type VII, α1                                                        | 2.53  | 2.0x10^2 | 1.26        | 8.29      | 6.58        |
| **DCLK1** | Doublecortin-like kinase 1                                                    | 2.69  | 1.6x10^3 | 1.21        | 4.91      | 4.06        |
| **DNM3**  | Dynamin 3                                                                     | 2.22  | 3.7x10^2 | 1.21        | 6.13      | 5.06        |
| **DYNCE1**| Dynein, cytoplasmic 1, intermediate chain 1                                   | 2.85  | 1.1x10^2 | 1.42        | 7.89      | 5.55        |
| **FOXO2** | Forkhead box A2                                                               | 2.18  | 6.2x10^2 | 1.36        | 5.56      | 4.09        |
| **GM6B**  | Glycoprotein M6B                                                              | 2.14  | 4.8x10^2 | 1.46        | 7.60      | 5.19        |
| **SPP1**  | Secreted phosphoprotein 1                                                      | 0.82  | 4.2x10^3 | 1.03        | 7.03      | 7.22        |
| **Unknown biological process**                                                      |                                     |       |          |             |           |             |
| **RNFL82**| Ring finger protein 182                                                       | 2.22  | 3.9x10^3 | 1.27        | 8.41      | 6.64        |
| **ACSS3** | Acyl-CoA synthetase short-chain family member 3                               | 2.48  | 3.3x10^3 | 1.28        | 6.52      | 5.08        |
| **GSTM4** | Glutathione S-transferase mu 4                                                 | 4.79  | 4.0x10^4 | 1.41        | 7.93      | 5.62        |
| **LINC00461**| Long intergenic non-protein coding RNA 461                                   | 4.67  | 6.0x10^4 | 1.55        | 9.31      | 5.99        |
| **FAM12A0**| Transmembrane protein 255A                                                    | 3.80  | 6.0x10^4 | 1.72        | 7.46      | 4.33        |
| **COL21A1**| Collagen, type XXI, α1                                                        | 4.49  | 4.0x10^4 | 1.74        | 7.61      | 4.38        |
| **METTL7A**| Methyltransferase like 7A                                                     | 3.32  | 5.0x10^3 | 1.49        | 8.06      | 5.40        |
| **GMPR**  | Guanosine monophosphate reductase                                             | 0.33  | 7.5x10^4 | 1.01        | 8.81      | 8.94        |
| **NID1**  | Nidogen 1                                                                     | 2.36  | 2.8x10^2 | 1.26        | 9.12      | 7.23        |
| **KIAA0895**| KIAA0895                                                                    | 2.04  | 5.5x10^2 | 1.21        | 6.57      | 5.44        |
| **C8orf4**| Chromosome 8 open reading frame 4                                             | 0.91  | 3.7x10^3 | 1.04        | 10.02     | 9.67        |
| **SEL13** | Sel-1 suppressor of lin-12-like 3 (Caenorhabditis elegans)                    | 2.19  | 4.3x10^2 | 1.33        | 8.99      | 6.76        |
| **GPC4**  | Glypican 4                                                                    | 2.55  | 2.2x10^3 | 1.41        | 8.55      | 6.07        |
| **PLEKHG1**| Plekstrin homology domain containing, family G (with RhoGef domain) member 1 | 2.47  | 2.8x10^2 | 1.38        | 6.36      | 4.62        |
with a previous study that detected a brain-specific isoform of PGC1α in the cytoplasm rather than the nucleus (27). It was also reported that the PGC1α isoform becomes localized in the mitochondria via phosphatase and tensin homolog-induced putative kinase 1 and voltage-dependent anion channel (28).

This present study also demonstrated that PGC1α was expressed in the mitochondria of GBM cells. Based on these

| Gene       | Description                                         | Score | P-value     | Fold-change | Up mean | Down mean |
|------------|-----------------------------------------------------|-------|-------------|-------------|---------|-----------|
| PIPOX      | Pipeolic acid oxidase                               | 3.29  | 4.0x10^4    | 1.68        | 6.46    | 3.84      |
| FAM65B     | Family with sequence similarity 65, member B        | 2.56  | 1.1x10^2    | 1.39        | 5.57    | 3.99      |
| C7orf57    | Chromosome 7 open reading frame 57                 | 2.17  | 4.2x10^2    | 1.46        | 5.56    | 3.80      |
| PPP2R2B    | Protein phosphatase 2, regulatory subunit B, β      | 3.58  | 2.8x10^3    | 1.61        | 7.44    | 4.62      |
| SERP2      | Stress-associated endoplasmic reticulum protein family member 2 | 2.11  | 5.2x10^2    | 1.22        | 6.19    | 5.09      |
| SOX2       | SRY (sex determining region Y)-box 2               | 1.23  | 2.5x10^1    | 1.04        | 4.07    | 3.92      |
| RPRM       | Reprimo, TP53 dependent G2 arrest mediator candidate | 0.43  | 6.9x10^1    | 1.01        | 3.99    | 4.04      |
| MFSD2A     | Major facilitator superfamily domain containing 2A | 3.69  | 2.0x10^3    | 1.30        | 7.33    | 5.63      |
| PELI2      | Pellino E3 ubiquitin protein ligase family member 2 | 2.91  | 1.1x10^2    | 1.29        | 7.33    | 5.68      |
| GCNT2      | Glucosaminyl (N-acetyl) transferase 2, I-branching enzyme (I blood group) | 2.40  | 3.3x10^2    | 1.22        | 7.59    | 6.22      |
| SLC16A4    | Solute carrier family 16, member 4                 | 2.88  | 1.1x10^2    | 1.39        | 8.00    | 5.77      |
| SH3BGR     | SH3 domain binding glutamic acid-rich protein       | 1.58  | 1.3x10^4    | 1.05        | 10.64   | 10.12     |
| WDR31      | WD repeat domain 31                                 | 3.54  | 2.8x10^3    | 1.20        | 5.83    | 4.86      |
| SLC16A9    | Solute carrier family 16, member 9                 | 2.07  | 4.4x10^1    | 1.23        | 6.40    | 5.19      |
| GSTT1      | Glutathione S-transferase theta 1                   | 2.91  | 1.3x10^3    | 1.40        | 7.41    | 5.31      |
| NDP        | Norrie disease (pseudogioma)                        | 2.53  | 2.4x10^2    | 1.50        | 7.62    | 5.09      |
| NDN        | Necdin, melanoma antigen (MAGE) family member       | 2.42  | 2.9x10^2    | 1.44        | 7.59    | 5.27      |
| ASB9       | Ankyrin repeat and SOCS box containing 9           | 2.20  | 4.3x10^2    | 1.26        | 7.03    | 5.58      |
| LONRF2     | LON peptidase N-terminal domain and ring finger 2   | 2.08  | 6.0x10^3    | 1.37        | 6.10    | 4.44      |
| SPHAR      | S-phase response (cyclin related)                   | 2.62  | 1.8x10^1    | 1.22        | 7.49    | 6.12      |
| RNF144A    | Ring finger protein 144A                            | 2.62  | 1.6x10^2    | 1.24        | 7.07    | 5.71      |
| SERINC5    | Serine incorporator 5                               | 4.07  | 1.4x10^3    | 1.20        | 10.73   | 8.95      |
| RRAGD      | Ras-related GTP binding D                          | 2.42  | 3.0x10^2    | 1.28        | 8.29    | 6.48      |
| OGDH1      | Oxoglutarate dehydrogenase-like                     | 2.65  | 1.5x10^2    | 1.25        | 6.36    | 5.11      |
| CEND1      | Cell cycle exit and neuronal differentiation 1      | 3.91  | 1.0x10^3    | 1.24        | 6.38    | 5.14      |
| RBPMS2     | RNA binding protein with multiple splicing 2        | 2.11  | 4.6x10^2    | 1.26        | 6.34    | 5.03      |
| SULF2      | Sulfatase 2                                        | 2.69  | 1.9x10^2    | 1.50        | 8.01    | 5.33      |
| MMP7       | Matrix metalloproteinase 7 (matrilysin, uterine)    | 2.97  | 2.0x10^1    | 1.24        | 5.14    | 4.15      |
| SLC2A12    | Solute carrier family 2 (facilitated glucose transporter), member 12 | 2.95  | 8.4x10^3    | 1.35        | 6.31    | 4.67      |
| GFTPT2     | Glutamine-fructose-6-phosphate transaminase 2      | 2.24  | 3.7x10^2    | 1.29        | 8.35    | 6.46      |
| SOX9       | SRY (sex determining region Y)-box 9               | 2.18  | 4.3x10^2    | 1.31        | 9.42    | 7.17      |
| C5orf46    | Chromosome 5 open reading frame 46                 | 2.29  | 3.2x10^2    | 1.34        | 8.92    | 6.67      |
| CP         | Ceruloplasmin (ferroxidase)                         | 2.35  | 3.3x10^2    | 1.05        | 4.24    | 4.03      |
| GPNMB      | Glycoprotein (transmembrane) mnb                    | 2.85  | 1.1x10^2    | 1.35        | 10.04   | 7.46      |
| SERPINI1   | Serpin peptidase inhibitor, clade I (neuroserpin), member 1 | 2.35  | 3.5x10^2    | 1.32        | 7.42    | 5.63      |
| TPRG1      | Tumor protein p63 regulated 1                      | 2.36  | 3.5x10^2    | 1.30        | 5.12    | 3.94      |
| PITX2      | Paired-like homeodomain 2                          | 2.09  | 5.6x10^2    | 1.32        | 5.44    | 4.13      |

*Up, and down mean refers to the mean of the specific gene expression levels in the ten most PGC1α up- or downregulated cell lines.*
corroborating results, it is predicted that PGC1α-mediated mitochondrial biogenesis and respiration is increased in GBM cells.

To investigate the role PGC1α has in GBM cells, several bioinformatics analyses were performed. The analyses demonstrated that metabolic and mitochondrial genes were highly correlated with PGC1α in a number of GBM cell lines. Class Neighbors analysis classified PGC1α-expressing GBM cell lines into two groups: Class A and B. Class A contained genes associated with development, neurogenesis, cell structure

| Functional role                        | Genes | P-value | -Log (P-value) |
|----------------------------------------|-------|---------|----------------|
| **Biological process**                 |       |         |                |
| Developmental processes                | 28    | 4.30x10^-6 | 5.37           |
| Ectoderm development                   | 13    | 2.10x10^-4 | 3.68           |
| Neurogenesis                           | 12    | 2.50x10^-4 | 3.60           |
| Cell structure and motility            | 13    | 1.20x10^-2 | 1.92           |
| Mesoderm development                   | 8     | 2.70x10^-2 | 1.57           |
| Cell structure                         | 8     | 5.80x10^-2 | 1.24           |
| Signal transduction                    | 25    | 6.60x10^-2 | 1.18           |
| Cell communication                     | 11    | 9.40x10^-2 | 1.03           |
| **Cellular component**                 |       |         |                |
| Extracellular region part              | 16    | 1.30x10^-4 | 3.89           |
| Extracellular region                   | 23    | 5.70x10^-4 | 3.24           |
| Extracellular matrix                   | 8     | 2.30x10^-3 | 2.64           |
| Extracellular space                    | 11    | 3.20x10^-2 | 2.49           |
| Proteinaceous extracellular matrix     | 7     | 6.90x10^-3 | 2.16           |

The dataset of significantly changed genes were identified using the Database for Annotation, Visualization and Integrated Discovery (DAVID; http://david.abcc.ncifcrf.gov) (P<0.05).

Figure 5. Bioinformatics analysis of PGC1α-associated genes in two classes of GBM cell lines. (A) Two-way hierarchical clustering of differentially expressed genes in the top ten PGC1α up- and downregulated GBM cell lines by Pearson distance. (B) Class A genes were divided into biological processes, molecular functions or cellular components. Color in the heat-maps displays expression relative to the mean expression value, with red indicating higher expression and blue lower expression. GBM, glioblastoma multiforme; PGC1α, peroxisome proliferator-activated receptor γ; coactivator 1α.
Table VII. List of class B genes highly expressed in peroxisome proliferator-activated receptor γ coactivator 1α downregulated glioblastoma multiforme cells.

| Gene             | Description                                      | Score | P-value  | Fold-change | Up mean | Down mean |
|------------------|--------------------------------------------------|-------|----------|-------------|---------|-----------|
| Major histocompatibility complex, class II-mediated immunity | Major histocompatibility complex, class II, DM α | 2.32  | 3.4x10²  | 1.34        | 5.69    | 7.66      |
| HLA-DM            |                                                  |       |          |             |         |           |
| HLA-DRA1          | Major histocompatibility complex, class II, DR β 1| 2.18  | 4.5x10²  | 1.35        | 5.99    | 8.08      |
| HLA-DQB1          | Major histocompatibility complex, class II, DQ β 1| 2.22  | 3.6x10²  | 1.26        | 5.16    | 6.49      |
| Signal transduction | ADAMTS1, 1 ADAM metallopeptidase with thrombospondin type 1 motif, 1 | 1.16  | 1.2x10¹  | 1.10        | 3.49    | 3.83      |
| ADAMTS6           | ADAM metallopeptidase with thrombospondin type 1 motif, 6 | 2.16  | 2.1x10²  | 1.31        | 4.71    | 6.17      |
| ARAP2             | ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 2 | 2.16  | 4.9x10²  | 1.27        | 4.51    | 5.74      |
| BAIP2LI           | BAI1-associated protein 2-like 1                 | 2.13  | 5.1x10²  | 1.22        | 5.84    | 7.10      |
| CD33              | CD33 molecule                                    | 2.54  | 6.6x10³  | 1.24        | 4.54    | 5.64      |
| DEPDC7            | DEP domain containing 7                          | 2.13  | 5.0x10²  | 1.23        | 6.86    | 8.47      |
| FCRLB             | FC receptor-like B                               | 2.89  | 1.3x10²  | 1.23        | 5.38    | 6.60      |
| RAB3B             | RAB3B, member RAS oncogene family                | 2.75  | 1.1x10²  | 1.39        | 4.80    | 6.68      |
| SLITRK5           | SLIT and NTRK-like family, member 5              | 2.59  | 1.6x10²  | 1.29        | 5.21    | 6.70      |
| ADRB2             | Adrenoceptor β 2, surface                        | 3.28  | 4.2x10³  | 1.34        | 5.85    | 7.85      |
| AHR1              | Aryl-hydrocarbon receptor repressor             | 2.06  | 5.5x10²  | 1.25        | 6.24    | 7.83      |
| CALB2             | Calbindin 2                                      | 2.46  | 1.7x10²  | 1.36        | 4.57    | 6.23      |
| F2RL2             | Coagulation factor II (thrombin) receptor-like 2 | 2.24  | 3.4x10²  | 1.39        | 4.33    | 6.04      |
| FGF1              | Fibroblast growth factor 1 (acidic)             | 2.06  | 5.0x10²  | 1.31        | 4.35    | 5.69      |
| GRB14             | Growth factor receptor-bound protein 14         | 2.08  | 4.8x10²  | 1.25        | 4.24    | 5.29      |
| IL12A             | Interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte Maturation factor 1, p35) | 3.58  | 1.8x10³  | 1.26        | 4.24    | 5.35      |
| IL4R              | Interleukin 4 receptor                           | 2.50  | 1.7x10²  | 1.21        | 5.42    | 6.54      |
| OR51B4            | Olfactory receptor, family 51, subfamily B, member 4 | 2.43  | 6.0x10³  | 1.23        | 4.25    | 5.22      |
| OXTR              | Oxytocin receptor                                | 2.29  | 2.8x10²  | 1.31        | 5.90    | 7.70      |
| PLCB4             | Phospholipase C, β 4                            | 2.66  | 1.9x10²  | 1.31        | 6.48    | 8.50      |
| PDGFA             | Platelet-derived growth factor α polypeptide    | 2.29  | 3.6x10²  | 1.26        | 6.68    | 8.43      |
| PTPN22            | Protein tyrosine phosphatase, non-receptor type 22 (lymphoid) | 2.79  | 1.3x10²  | 1.29        | 3.60    | 4.65      |
| RGS10             | Regulator of G-protein signaling 10              | 2.96  | 5.8x10³  | 1.19        | 8.25    | 9.83      |
| STYK1             | Serine/threonine/tyrosine kinase 1              | 2.25  | 1.9x10²  | 1.25        | 4.15    | 5.17      |
| SPHK1             | Sphingosine kinase 1                            | 2.05  | 5.2x10²  | 1.20        | 6.57    | 7.86      |
| STC2              | Stanniocalcin 2                                  | 2.12  | 4.9x10²  | 1.23        | 7.08    | 8.68      |
| WNT5B             | Wingless-type MMTV integration site family, member 5B | 3.11  | 7.4x10³  | 1.32        | 5.19    | 6.84      |

Intracellular signaling cascade

| DEPDC7          | DEP domain containing 7 | 2.13  | 5.0x10²  | 1.23        | 6.86    | 8.47      |
| RAB3B           | RAB3B, member RAS oncogene family | 2.75  | 1.1x10²  | 1.39        | 4.80    | 6.68      |
| ADRB2           | Adrenoceptor β 2, surface | 3.28  | 4.2x10³  | 1.34        | 5.85    | 7.85      |
| AHR1            | Aryl-hydrocarbon receptor repressor | 2.06  | 5.5x10²  | 1.25        | 6.24    | 7.83      |
| CALB2           | Calbindin 2             | 2.46  | 1.7x10²  | 1.36        | 4.57    | 6.23      |
| FGF1            | Fibroblast growth factor 1 (acidic)             | 2.06  | 5.0x10²  | 1.31        | 4.35    | 5.69      |
Table VII. Continued.

| Gene    | Description                                                                 | Score | P-value       | Fold-change mean | Up\textsuperscript{a} mean | Down\textsuperscript{a} mean |
|---------|-----------------------------------------------------------------------------|-------|----------------|------------------|-----------------------------|-----------------------------|
| **Fold-Up\textsuperscript{a}** |                                                                             |       |                |                  |                             |                             |
| **IL12A** | Interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte Maturation factor 1, p35) | 3.58  | 1.8x10\textsuperscript{3} | 1.26            | 4.24                       | 5.35                       |
| **IL4R**   | Interleukin 4 receptor                                                      | 2.50  | 1.7x10\textsuperscript{2} | 1.21            | 5.42                       | 6.54                       |
| **OXTR**   | Oxytocin receptor                                                          | 2.29  | 2.8x10\textsuperscript{2} | 1.31            | 5.90                       | 7.70                       |
| **PLCB4**  | Phospholipase C, β 4                                                      | 2.66  | 1.9x10\textsuperscript{2} | 1.31            | 6.48                       | 8.50                       |
| **PDGFA**  | Platelet-derived growth factor α polypeptide                               | 2.29  | 3.6x10\textsuperscript{2} | 1.26            | 6.68                       | 8.43                       |
| **Cell surface receptor mediated signal transduction** |                                                               |       |                |                  |                             |                             |
| **ARAP2**  | ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 2                 | 2.16  | 4.9x10\textsuperscript{2} | 1.27            | 4.51                       | 5.74                       |
| **CD33**   | CD33 molecule                                                              | 2.54  | 6.6x10\textsuperscript{02} | 1.24            | 4.54                       | 5.64                       |
| **SLITRK5**| SLIT and NTRK-like family, member 5                                        | 2.59  | 1.6x10\textsuperscript{02} | 1.29            | 5.21                       | 6.70                       |
| **ADRB2**  | Adrenoceptor β 2, surface                                                  | 3.28  | 4.2x10\textsuperscript{01} | 1.34            | 5.85                       | 7.85                       |
| **F2RL2**  | Coagulation factor II (thrombin) receptor-like 2                           | 2.24  | 3.4x10\textsuperscript{01} | 1.39            | 4.33                       | 6.04                       |
| **FGF1**   | Fibroblast growth factor 1 (acidic)                                       | 2.06  | 5.0x10\textsuperscript{02} | 1.31            | 4.35                       | 5.69                       |
| **GRB14**  | Growth factor receptor-bound protein 14                                    | 2.08  | 4.8x10\textsuperscript{02} | 1.25            | 4.24                       | 5.29                       |
| **IL12A**  | Interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte maturation factor 1, p35) | 3.58  | 1.8x10\textsuperscript{3} | 1.26            | 4.24                       | 5.35                       |
| **Down\textsuperscript{a}** |                                                                             |       |                |                  |                             |                             |
| **IL4R**   | Interleukin 4 receptor                                                      | 2.50  | 1.7x10\textsuperscript{01} | 1.21            | 5.42                       | 6.54                       |
| **OR51B4** | Olfactory receptor, family 51, subfamily B, member 4                       | 2.43  | 6.0x10\textsuperscript{01} | 1.23            | 4.25                       | 5.22                       |
| **OXTR**   | Oxytocin receptor                                                          | 2.29  | 2.8x10\textsuperscript{01} | 1.31            | 5.90                       | 7.70                       |
| **PDGFA**  | Platelet-derived growth factor α polypeptide                               | 2.29  | 3.6x10\textsuperscript{02} | 1.26            | 6.68                       | 8.43                       |
| **PTPN22** | Protein tyrosine phosphatase, non-receptor type 22 (lymphoid)              | 2.79  | 1.3x10\textsuperscript{01} | 1.29            | 3.60                       | 4.65                       |
| **RGS10**  | Regulator of G-protein signaling 10                                        | 2.96  | 5.8x10\textsuperscript{01} | 1.19            | 8.25                       | 9.83                       |
| **STYK1**  | Serine/threonine/tyrosine kinase 1                                         | 2.25  | 1.9x10\textsuperscript{01} | 1.25            | 4.15                       | 5.17                       |
| **STC2**   | Stanniocalcin 2                                                            | 2.12  | 4.9x10\textsuperscript{01} | 1.23            | 7.08                       | 8.68                       |
| **T-cell mediated immunity** |                                                             |       |                |                  |                             |                             |
| **FOSL1**  | FOS-like antigen 1                                                         | 2.36  | 3.2x10\textsuperscript{01} | 1.25            | 7.99                       | 9.99                       |
| **IL12A**  | Interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte maturation factor 1, p35) | 3.58  | 1.8x10\textsuperscript{3} | 1.26            | 4.24                       | 5.35                       |
| **HLA-DMA** | Major histocompatibility complex, class II, DM α                           | 2.32  | 3.4x10\textsuperscript{01} | 1.34            | 5.69                       | 7.66                       |
| **HLA-DRB1** | Major histocompatibility complex, class II, DR β 1                       | 2.18  | 4.5x10\textsuperscript{01} | 1.35            | 5.99                       | 8.08                       |
| **HLA-DQB1** | Major histocompatibility complex, class II, DQ β 1                       | 2.22  | 3.6x10\textsuperscript{01} | 1.26            | 5.16                       | 6.49                       |
| **Ligand-mediated signaling** |                                                             |       |                |                  |                             |                             |
| **ADRB2**  | Adrenoceptor β 2, surface                                                  | 3.28  | 4.2 x10\textsuperscript{01} | 1.34            | 5.85                       | 7.85                       |
| **AHRR**   | Aryl-hydrocarbon receptor repressor                                         | 2.06  | 5.5 x10\textsuperscript{01} | 1.25            | 6.24                       | 7.83                       |
| **FGF1**   | Fibroblast growth factor 1 (acidic)                                       | 1.37  | 1.9x10\textsuperscript{01} | 1.03            | 3.89                       | 4.00                       |
| **IL12A**  | Interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte Maturation factor 1, p35) | 3.58  | 1.8x10\textsuperscript{01} | 1.26            | 4.24                       | 5.35                       |
| **IL4R**   | Interleukin 4 receptor                                                      | 2.50  | 1.7x10\textsuperscript{01} | 1.21            | 5.42                       | 6.54                       |
| **PDGFA**  | Platelet-derived growth factor α polypeptide                               | 2.29  | 3.6x10\textsuperscript{02} | 1.26            | 6.68                       | 8.43                       |
| **WNT5B**  | Wingless-type MMTV integration site family, member 5B                      | 3.11  | 7.4x10\textsuperscript{01} | 1.32            | 5.19                       | 6.84                       |
Table VII. Continued.

| Gene                  | Description                                                                 | Score | P-value | Fold-change | Up mean | Down mean |
|-----------------------|-----------------------------------------------------------------------------|-------|---------|-------------|---------|-----------|
| Calcium mediated     |                                                                             |       |         |             |         |           |
| signaling             |                                                                             |       |         |             |         |           |
| ADRB2                 | Adrenoceptor β 2, surface                                                   | 3.28  | 4.2x10³ | 1.34        | 5.85   | 7.85      |
| CALB2                 | Calbindin 2                                                                 | 2.46  | 1.7x10² | 1.36        | 4.57   | 6.23      |
| OXTR                  | Oxytocin receptor                                                           | 2.29  | 2.8x10² | 1.31        | 5.90   | 7.70      |
| PDGFA                 | Platelet-derived growth factor α polypeptide                               | 2.29  | 3.6x10² | 1.26        | 6.68   | 8.43      |
| Oncogenesis-associated|                                                                             |       |         |             |         |           |
| MAGEA1                | Melanoma antigen family A, 1 (directs expression of antigen MZ2-E)          | 1.55  | 1.3x10² | 1.36        | 4.60   | 6.23      |
| MAGEA11               | Melanoma antigen family A, 11                                              | 2.88  | 1.2x10² | 1.72        | 3.70   | 6.37      |
| MAGEC2                | Melanoma antigen family C, 2                                               | 2.06  | 4.3x10² | 1.35        | 5.44   | 7.34      |
| Cell communication    |                                                                             |       |         |             |         |           |
| ADAMTS1               | ADAM metallopeptidase with thrombospondin type 1 motif, 1                  | 1.16  | 1.2x10¹ | 1.10        | 3.49   | 3.83      |
| ADAMTS6               | ADAM metallopeptidase with thrombospondin type 1 motif, 6                  | 2.16  | 2.1x10² | 1.31        | 4.71   | 6.17      |
| CD33                  | CD33 molecule                                                               | 2.54  | 6.6x10² | 1.24        | 4.54   | 5.64      |
| ADRB2                 | Adrenoceptor β 2, surface                                                   | 3.28  | 4.2x10³ | 1.34        | 5.85   | 7.85      |
| AHRR                  | Aryl-hydrocarbon receptor repressor                                         | 2.06  | 5.5x10² | 1.25        | 6.24   | 7.83      |
| FGF1                  | Fibroblast growth factor 1 (acidic)                                         | 1.37  | 1.9x10¹ | 1.03        | 3.89   | 4.00      |
| IL12A                 | Interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic        | 3.58  | 1.8x10³ | 1.26        | 4.24   | 5.35      |
| lymphocyte Maturation factor 1, p35) |                                                                             |       |         |             |         |           |
| IL4R                  | Interleukin 4 receptor                                                      | 2.50  | 1.7x10² | 1.21        | 5.42   | 6.54      |
| PDGFA                 | Platelet-derived growth factor α polypeptide                               | 2.29  | 3.6x10² | 1.26        | 6.68   | 8.43      |
| PTPN22                | Protein tyrosine phosphatase, non-receptor type 22 (lymphoid)              | 2.79  | 1.3x10² | 1.29        | 3.60   | 4.65      |
| WNT5B                 | Wingless-type MMTV integration site family, member 5B                      | 3.11  | 7.4x10³ | 1.32        | 5.19   | 6.84      |
| Unknown biological    |                                                                             |       |         |             |         |           |
| process               |                                                                             |       |         |             |         |           |
| FST                   | Follistatin                                                                 | 2.56  | 2.2x10² | 1.36        | 6.21   | 8.43      |
| SMTN                  | Smoothelin                                                                  | 1.99  | 6.6x10² | 1.03        | 3.75   | 3.63      |
| AOX1                  | Aldehyde oxidase 1                                                          | 4.61  | 2.0x10⁴ | 1.59        | 4.65   | 7.38      |
| SH2D5                 | SH2 domain containing 5                                                     | 3.37  | 1.8x10³ | 1.26        | 4.95   | 6.24      |
| KIAA1609              | TBC/LysM-associated domain containing 1                                     | 4.08  | 6.0x10⁴ | 1.26        | 5.66   | 7.14      |
| VEPH1                 | Ventricular zone expressed PH domain-containing 1                           | 2.10  | 4.4x10² | 1.24        | 5.03   | 6.24      |
| MEOX2                 | Mesenchyme homeobox 2                                                        | 2.34  | 9.0x10⁴ | 1.37        | 3.34   | 4.58      |
| BATF3                 | Basic leucine zipper transcription factor, ATF-like 3                        | 2.53  | 1.9x10² | 1.20        | 5.86   | 7.06      |
| KRT34                 | Keratin 3                                                                  | 2.89  | 2.0x10⁴ | 1.36        | 3.86   | 5.25      |
| ST6GALNAC5            | ST6 (α-N-acetyl-neuraminyl-2,3-β-galactosyl-1,3)-N-acetylgalactosaminide α2,6-sialyltransferase 5 | 2.39  | 2.5x10² | 1.40        | 3.93   | 5.50      |
| SERPINB7              | Serpin peptidase inhibitor, clade B (ovalbumin), member 7                   | 2.05  | 5.9x10² | 1.46        | 4.92   | 7.18      |
| CRISPLD2              | Cysteine-rich secretory protein LCCL domain containing 2                    | 2.49  | 2.4x10² | 1.22        | 5.83   | 7.14      |
| LOC644656             | Uncharacterized LOC644656                                                   | 4.97  | 4.0x10⁴ | 1.22        | 5.94   | 7.25      |
| FRMD6-AS1             | FRMD6 antisense RNA 1                                                       | 3.57  | 2.2x10³ | 1.21        | 5.11   | 6.19      |
| Gene        | Description                                      | Score | P-value | Fold-change | Up\(^a\) mean | Down\(^a\) mean |
|------------|--------------------------------------------------|-------|---------|-------------|---------------|----------------|
| **MGCL**   | Monoglyceride lipase                             | 3.50  | 2.6x10\(^3\) | 1.27 | 7.44 | 9.49 |
| **CYP2R1** | Cytochrome P450, family 2, subfamily R, polypeptide | 2.47  | 2.5x10\(^2\) | 1.30 | 6.37 | 8.25 |
| **C11orf41** | 1 KIAA1549-like                               | 2.16  | 4.2x10\(^3\) | 1.21 | 4.64 | 5.62 |
| **LOC389906** | Zinc finger protein 839 pseudogene             | 2.01  | 6.2x10\(^2\) | 1.36 | 5.07 | 6.89 |
| **ATP8B1** | ATPase, aminophospholipid transporter, class I, type 8B, member 1 | 2.75  | 1.7x10\(^2\) | 1.35 | 6.06 | 8.21 |
| **EXT1**   | Exostosin glycosyltransferase 1                 | 3.64  | 1.4x10\(^3\) | 1.20 | 9.00 | 10.82 |
| **APCDD1L** | Adenomatosis polyposis coli downregulated 1-like | 2.30  | 3.5x10\(^2\) | 1.27 | 5.46 | 6.92 |
| **LOC100506325** | Uncharacterized LOC100506325     | 4.38  | 4.2x10\(^2\) | 1.21 | 4.64 | 5.62 |
| **C11orf41** | 1 KIAA1549-like                               | 3.44  | 4.8x10\(^3\) | 1.52 | 4.17 | 6.34 |
| **LOC100506325** | Uncharacterized LOC100506325     | 2.78  | 1.3x10\(^2\) | 1.43 | 4.34 | 6.21 |
| **PARP8**  | Poly (ADP-ribose) polymerase family, member 8  | 2.52  | 2.3x10\(^2\) | 1.22 | 5.07 | 6.20 |
| **UGT8**   | UDP glycosyltransferase 8                        | 2.18  | 4.3x10\(^2\) | 1.28 | 5.39 | 6.91 |
| **LOC730755** | LOC730755                                      | 2.39  | 3.2x10\(^3\) | 1.55 | 4.44 | 6.87 |
| **HBE1**   | Hemoglobin, epsilon 1                           | 2.56  | 1.7x10\(^2\) | 1.48 | 4.71 | 6.98 |
| **MPP4**   | Membrane protein, palmitoylated 4 (MAGUK p55 subfamily member 4) | 2.89  | 1.6x10\(^3\) | 1.42 | 3.50 | 4.96 |
| **CSTA**   | Cystatin A (stefin A)                            | 2.04  | 4.5x10\(^2\) | 1.39 | 3.80 | 5.29 |
| **SRGN**   | Serglycin                                       | 2.40  | 2.7x10\(^2\) | 1.45 | 7.05 | 10.24 |
| **LOC100506465** | Uncharacterized LOC100506465 | 2.55  | 1.7x10\(^2\) | 1.30 | 4.40 | 5.72 |
| **MOK**    | MOK protein kinase                               | 2.00  | 5.8x10\(^2\) | 1.21 | 6.81 | 8.25 |
| **INPP4B** | Inositol polypophosphate-4-phosphatase, type II, 105 kDa | 2.59  | 2.0x10\(^2\) | 1.37 | 5.53 | 7.60 |
| **AFAP1L1** | Actin filament associated protein 1-like 2      | 2.21  | 3.9x10\(^2\) | 1.23 | 4.77 | 5.87 |
| **CCBE1**  | Collagen and calcium binding EGF domains 1      | 2.07  | 5.5x10\(^2\) | 1.37 | 4.55 | 6.25 |
| **KCNK1**  | Potassium channel, subfamily K, member 1         | 1.49  | 2.2x10\(^1\) | 1.22 | 3.76 | 4.61 |
| **CCND2**  | Cyclin D2                                       | 2.31  | 1.5x10\(^2\) | 1.35 | 3.98 | 5.36 |
| **CDA**    | Cytidine deaminase                               | 1.43  | 1.6x10\(^1\) | 1.04 | 7.58 | 7.86 |
| **DMKN**   | Dermokine                                       | 2.03  | 5.7x10\(^2\) | 1.36 | 4.52 | 6.16 |
| **NOG**    | Noggin                                          | 2.06  | 5.1x10\(^2\) | 1.44 | 4.04 | 5.82 |
| **GTF51**  | Gametocyte specific factor 1                    | 2.02  | 6.6x10\(^2\) | 1.59 | 4.07 | 6.47 |
| **NT5E**   | 5'-nucleotidase, ecto (CD73)                    | 2.73  | 1.2x10\(^2\) | 1.24 | 8.11 | 10.04 |
| **BIRC3**  | Baculoviral IAP repeat containing 3             | 2.07  | 5.4x10\(^2\) | 1.24 | 4.88 | 6.05 |
| **NAP1L2** | Nucleosome assembly protein 1-like 2            | 2.47  | 2.3x10\(^2\) | 1.31 | 4.87 | 6.36 |
| **SLCO4A1** | Solute carrier organic anion transporter family, member 4A1 | 2.39  | 3.1x10\(^2\) | 1.30 | 6.35 | 8.26 |
| **KIAA1324L** | KIAA1324-like                     | 2.14  | 4.9x10\(^2\) | 1.19 | 4.75 | 5.66 |
| **CYP2J2** | Cytochrome P450, family 2, subfamily J, polypeptide 2 | 3.00  | 8.8x10\(^3\) | 1.28 | 4.13 | 5.27 |
| **TUBA3C** | Tubulin, α3c                                   | 2.44  | 2.7x10\(^2\) | 1.20 | 5.59 | 6.70 |
| **CTAG2**  | Cancer/testis antigen 2                        | 2.08  | 7.2x10\(^2\) | 1.35 | 3.85 | 5.21 |
| **GALNTL4** | UDP-N-acetyl-α-D-galactosamine: polypeptide-N-acetylgalactosaminyltransferase 18 | 2.52  | 2.2x10\(^02\) | 1.26 | 5.66 | 7.10 |
| **MGC16121** | MIR503 host gene (non-protein coding)           | 2.81  | 1.2x10\(^2\) | 1.25 | 5.74 | 7.18 |
| **COL3A1** | Collagen, type III, α1                         | 2.32  | 3.3x10\(^2\) | 1.53 | 5.05 | 7.74 |
| **PAPSS2** | 3'-phosphoadenosine 5'-phosphosulfate synthase 2 | 1.98  | 6.9x10\(^2\) | 1.25 | 7.17 | 8.98 |
| **BDNF-AS1** | BDNF antisense RNA                           | 2.91  | 9.6x10\(^3\) | 1.25 | 4.12 | 5.16 |
| **KRTAP1-5** | Keratin associated protein 1-5                 | 2.40  | 2.6x10\(^3\) | 1.37 | 4.06 | 5.55 |
| **CCDC80** | Coiled-coil domain containing 80               | 2.54  | 2.2x10\(^2\) | 1.29 | 6.78 | 8.73 |
| **NAP1L3** | Nucleosome assembly protein 1-like 3           | 2.06  | 5.6x10\(^2\) | 1.29 | 5.73 | 7.39 |
and motility. Class B contained genes associated with immunity, oncogenesis and signaling, including intracellular, T cell-mediated, ligand-mediated and calcium-mediated pathways. Class A genes are involved in mitochondrial and metabolic pathways, whilst class B genes are involved in differentiation and immune pathways. These data reinforce the hypothesis that PGC1α may have an important role in regulating mitochondrial and metabolic signaling pathways in the GBM microenvironment.

A notable result was the association of NDN with PGC1α. NDN is reported to function as a tumor suppressor in GBM and controls the proliferation of white adipose progenitor cells. NDN interacts with PGC1α via nicotinamide adenine dinucleotide-dependent protein deacetylase (Sirt-1) and two transcription factors, E2F1 and P53, suggesting that interactions with these cell cycle regulating factors are key to its function. Therefore, it is hypothesized that PGC1α

Table VII. Continued.

| Gene       | Description                       | Score | P-value | Fold-change | Up mean | Down mean |
|------------|-----------------------------------|-------|---------|-------------|---------|-----------|
| TMEM171    | Transmembrane protein 171         | 2.88  | 1.1x10^2| 1.40        | 4.45    | 6.22      |
| NAV3       | Neuron navigator 3                | 2.59  | 1.5x10^2| 1.33        | 5.05    | 6.70      |
| HIST1H4H   | Histone cluster 1, H4h            | 2.50  | 1.5x10^2| 1.21        | 4.38    | 5.30      |
| FCRLB      | Fc receptor-like B                | 2.89  | 1.3x10^2| 1.23        | 5.38    | 6.60      |
| CSPG4      | Chondroitin sulfate proteoglycan 4| 2.54  | 2.3x10^2| 1.43        | 4.35    | 6.22      |
| LINCO0341I | Long intergenic non-protein coding RNA 341 | 1.97  | 7.1x10^2| 1.23        | 6.29    | 7.75      |
| GADI       | Glutamate decarboxylase 1 (brain, 67 kDa) | 2.12  | 5.5x10^2| 1.21        | 5.24    | 6.34      |

"Up", and down mean refers to the mean of the specific gene expression levels in the ten most PGC1α up- or downregulated cell lines. MHC, Major histocompatibility complex.

Table VIII. Annotated summary of class B of peroxisome proliferator-activated receptor γ, coactivator 1α.

| Biological process                        | Genes | P-value | -Log (P-value) |
|-------------------------------------------|-------|---------|----------------|
| MHCII-mediated immunity                   | 3     | 8.20x10^3| 2.09           |
| Signal transduction                       | 27    | 9.70x10^3| 2.01           |
| Intracellular signaling cascade           | 11    | 1.10x10^3| 1.96           |
| Cell surface receptor mediated signal transduction | 16    | 1.40x10^2| 1.85           |
| T-cell mediated immunity                  | 5     | 1.40x10^2| 1.85           |
| Ligand-mediated signaling                 | 7     | 1.60x10^2| 1.80           |
| Calcium mediated signaling                | 4     | 2.00x10^2| 1.70           |
| Other oncogenesis                         | 3     | 4.30x10^2| 1.37           |
| Cell communication                        | 11    | 6.90x10^3| 1.16           |
| MHC protein complex                       | 4     | 2.90x10^3| 2.54           |
| Extracellular matrix                      | 7     | 7.80x10^3| 2.11           |
| Extracellular region part                 | 12    | 8.40x10^3| 2.08           |
| MHC class II protein complex              | 3     | 9.30x10^3| 2.03           |
| Extracellular region                      | 18    | 2.10x10^2| 1.68           |
| Proteinaceous extracellular matrix        | 6     | 2.30x10^2| 1.64           |
| Apical plasma membrane                    | 4     | 2.90x10^2| 1.54           |
| Chromatin assembly complex                | 2     | 3.00x10^2| 1.52           |
| Microsome                                 | 5     | 3.20x10^2| 1.49           |
| Vesicular fraction                        | 5     | 3.50x10^2| 1.46           |
| Apical part of cell                       | 4     | 6.10x10^2| 1.21           |

The dataset of significantly changed genes were identified using the Database for Annotation, Visualization and Integrated Discovery (DAVID; http://david.abcc.ncifcrf.gov) (P<0.05). MHC, Major Histocompatibility Complex.
enhances antioxidant capacity in GBM by interacting with NDN and Sirt1, leading to delayed progression of necrosis and ultimately increasing overall patient survival. Future studies that elucidate the molecular interactions of PGC1α are required to derive improved insights into the diagnosis, prognosis and treatment of GBM.

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