Genomic and proteomic profiling II: Comparative assessment of gene expression profiles in leiomyomas, keloids, and surgically-induced scars
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Abstract

Background: Leiomyoma have often been compared to keloids because of their fibrotic characteristic and higher rate of occurrence among African Americans as compared to other ethnic groups. To evaluate such a correlation at molecular level this study comparatively analyzed leiomyomas with keloids, surgical scars and peritoneal adhesions to identify genes that are either commonly and/or individually distinguish these fibrotic disorders despite differences in the nature of their development and growth.

Methods: Microarray gene expression profiling and realtime PCR.

Results: The analysis identified 3 to 12% of the genes on the arrays as differentially expressed among these tissues based on P ranking at greater than or equal to 0.005 followed by 2-fold cutoff change selection. Of these genes about 400 genes were identified as differentially expressed in leiomyomas as compared to keloids/incisional scars, and 85 genes as compared to peritoneal adhesions (greater than or equal to 0.01). Functional analysis indicated that the majority of these genes serve as regulators of cell growth (cell cycle/apoptosis), tissue turnover, transcription factors and signal transduction. Of these genes the expression of E2F1, RUNX3, EGR3, TBPIP, ECM-2, ESM1, THBS1, GAS1, ADAM17, CST6, FBLN5, and COL18A was confirmed in these tissues using quantitative realtime PCR based on low-density arrays.

Conclusion: the results indicated that the molecular feature of leiomyomas is comparable but may be under different tissue-specific regulatory control to those of keloids and differ at the levels rather than tissue-specific expression of selected number of genes functionally regulating cell growth and apoptosis, inflammation, angiogenesis and tissue turnover.

Background
Leiomyomas are benign uterine tumors with unknown etiology that originate from transformation of myometrial smooth muscle cells and/or connective tissue fibroblasts during the reproductive years. Leiomyomas can develop in multiple numbers that are individually encapsulated by a connective tissue core separating them from the surrounding normal myometrium and are ovarian...
steroid-dependent for their growth. Although they occur independent of ethnicity, clinical and epidemiological studies have indicated that African Americans are at a higher risk of developing leiomyomas compared to other ethnic groups [1].

Leiomyomas have also often been compared to keloids because of a higher rate of occurrence in African Americans and their fibrotic characteristics despite differences in the nature of their development and growth [2]. Keloids are benign skin lesions that develop spontaneously, or form from proliferation of dermal cells following tissue injury resulting in a collagenous and poorly vascularized structure at later stage of their development [3-6]. Unlike surgically-induced and hypertrophic scars that are confined to the area of original tissue injury, keloids can expand beyond the boundaries of their original sites following removal and during healing. Keloids are rather similar to hypertrophic scars at early stages of development, however they become collagenous and poorly vascularized at later stages and tend to occur more frequently in darker skinned individuals [3,4]. Surgically-induced injury and/or inflammation also result in peritoneal scar or adhesions and similar to other incisional scars they are confined to the area of tissue injury[7]. Peritoneal adhesions also display a considerable histological similarity with dermal scars; however there is no data to suggest a higher risk of adhesion formation with ethnicity. Comparatively, uterine tissue injury i.e., following myomectomy or cesarean sections, does not cause leiomyomas formation, but rather results in incisional scar formation at the site of injury. Furthermore, leiomyomas consist mainly of smooth muscle cells forming a relatively vascularized tissue, while keloids derive from proliferation of connective tissue fibroblasts, adopting a myofibroblastic phenotype at a later stage of wound healing[3,4].

As part of these characteristics previous studies have identified excess production and deposition of extracellular matrix, namely collagens in leiomyomas, keloids, hypertrophic and surgical scars and peritoneal adhesions [2,7-10]. Evidence also exists implicating altered production of several proinflammatory and profibrotic cytokines, proteases and adhesion molecules in pathogenesis and characteristic of these and other fibrotic disorders [11-14]. Large-scale gene expression studies have provided additional evidence for the expression of a number of differentially expressed genes in leiomyomas [11,15-17], keloids and hypertrophic scars [15,16] as compared to their respective normal tissues. Several conventional studies have demonstrated that the products of some of these genes regulate various cellular activities implicated in the outcome of tissue fibrosis at various sites throughout the body Among these genes, include several growth factors and cytokines such as TGF-β system, proteases, adhesion molecules and extracellular matrix etc. (for review see [7-17]). Despite these advancements, the biological significance of many of these genes in pathophysiology of leiomyomas and keloids and their relationship to the outcome of other tissue fibrosis remains to be established. In addition, there has not been any study that comparatively analyzed the molecular profile that distinguishes leiomyomas from other fibrotic tissues, specifically keloids.

Considering these characteristics we used large-scale gene expression profiling to evaluate such a correlation at molecular level by comparatively analyzing leiomyomas with keloids, surgical scars and peritoneal adhesions to identify genes that are either commonly and/or individually distinguish these fibrotic disorders despite differences in nature of their development and growth. We evaluated the expression of 12 genes in these tissues representing several functional categories important to tissue fibrosis using quantitative realtime PCR based on low-density arrays.

Methods

All the materials and methods utilized in this study are identical to our previous studies and those reported in the accompanying manuscript [11,17]. Prior approval was obtained from the University of Florida Institutional Review Board for the experimental protocol of this study, with patients with scars giving informed consent, while the study with leiomyomas was expedited and did require obtaining written informed consent.

Total cellular RNA was isolated from keloid/incisional scars (N = 4) and subjected to microarray analysis using human U133A Affymetrix GeneChips as described in the accompanying manuscript [17]. One patient who had developed keloid at the site of previous surgical incision also developed leiomyoma. All the patients with keloids and one patient with incisional scar were African Americans. In addition, we utilized the gene expression data obtained from our previous study [11] involving leiomyomas (N = 3) and peritoneal adhesions (N = 3) using human U95A GeneChips. These tissues were from Caucasians patients with the exception of one peritoneal adhesion collected from an African American patient. The age of patients with leiomyomas ranged from 29 to 38 years. These women were not taking any medication, including hormonal therapy, for previous 3 months prior to surgery and based on their last menstrual period and endometrial histology was from early to mid-secretory phase of the menstrual cycle. The age of patients with adhesions ranged from 25 to 46 years and those with keloids and surgical scars were 26, 32 and 39 years, respectively. All the tissues with the exception of one keloid matched by their corresponding normal tissues i.e. myometrium, skin and pari-
atal peritoneum for microarray analysis. All the procedures for total RNA isolation, amplification, cDNA synthesis, RNA labeling and hybridization into the GeneChips were carried out as previously described in detail [11].

**Microarray data analysis**

The gene expression values obtained from the leiomyomas and matched myometrium (N = 6) using U133A GeneChips in the accompanying manuscript was utilized here only for the purpose of comparative analysis. The gene expression values obtained from all U133A and U95A GeneChips were independently subjected to global normalization and transformation, and their coefficient of variation was calculated for each probe set across the chips as previously described [11]. The selected gene expression values were than subjected to supervised learning including statistical analysis in R programming and ANOVA with Turkey test and gene ranking at P ≤ 0.005 followed by 2-fold change cutoff[11]. Functional annotation and molecular pathway analysis was carried out as described [17].

For combining the data from the U95A and U133A chips the probes that were absent across all chips were removed and subjected to t-test to identify differentially expressed genes. The data set was annotated using Entrez Gene and full annotation files NetAffy software and probe sets were consolidated based on Entrez Gene ID and subjected to microarray.dog.MetaAnalysisTester. The analysis keeps one probe for each gene with the smallest p-value for up or down t-test. The probe with smallest p-value for up regulated genes may be different from probe sets with smallest p-value for down-regulated genes. When the data from U95A and U133A was combined if a gene was represented on one platform, but not on both the missing data was replaced with NA. The data was subjected to Fisher combine p-values using inverse chi-square method and permutation test to determine new p-value, named randomized inverse chi-square p-value and to calculate the traditional inverse chi-square p-value. The false discovery rate was calculated using the inverse chi-square p-value and the min t-test p-value for each gene.

**Quantitative realtime PCR**

The same total RNA isolated from these tissues and used for microarray studies was also subjected to quantitative realtime PCR using custom-made TaqMan Low Density Arrays (LDAs) assessing the expression of 12 genes and the house-keeping gene, GAPDH. Detailed descriptions of LDA and realtime PCR, including data analysis has been provided in the accompanied manuscript[17].

**Results**

**Gene expression profiles of leiomyomas, keloids and scars**

Utilizing Affymetrix U133A platform we first assessed the gene expression profile of keloids and incisional scars. Following supervised and unsupervised assessments of the gene expression values in each cohort the combined data set with the gene expression values of leiomyomas reported in the accompanying manuscript using U133A arrays [17] only for the purpose of comparative analysis. The analysis based on supervised and unsupervised assessment and P ranking of P < 0.005, followed by 2-fold cutoff change selection, resulted in identification of 1124 transcripts (1103 genes) of which 732 genes were over-expressed and 371 were under-expressed in leiomyomas as compared to keloids/incisional scars (N = 4). Hierarchical clustering separated these genes into distinctive groups with each cohort clustering into the corresponding subgroup (Fig. 1). A partial list of these differentially expressed genes with their biological functions is shown in Tables 1 and 2. The combined gene list presented in Tables 1 and 2 is different from the list reported in the accompanying manuscript for leiomyomas[17], although many commonly expressed genes displaying different expression values could be find in between the tables.

The analysis based on inclusion of leiomyomas as two independent cohorts (3 A. American and 3 Caucasians) resulted in identification of a limited number of differentially expressed genes as compared to keloids (N = 2)/incisional scars (N = 2). Because both keloids were from A. American patients we excluded one of the incisional scar from a Caucasian patient from the analysis and lowered the statistical stringency to P < 0.01 which resulted in identified 424 differentially expressed genes in A. American leiomyomas as compared to keloids/scars. Similar analysis resulted in identified 393 differentially expressed genes in Caucasian leiomyomas as compared to keloids/scars (all from A. Americans). Of these genes 64 and 32 genes, respectively differed by at least 2 fold in leiomomas of AA and Caucasians, compared to keloids/incisional scars (Table 3).

We also utilized the gene expression values obtained in our previous microarray studies in leiomyomas[11] and peritoneal adhesions (unpublished results) for comparative analysis. Because these results were generated using Affymetrix U95A GeneChips, due to cross-platform comparability with U133A the combined data from both platforms were subjected to additional analysis as described in the materials and methods. The analysis based on p < 0.005 and 2-fold change cutoff identified 1801 genes as over-expressed and 45 under-expressed in leiomyomas as compared to keloids/incisional scars and peritoneal adhesions (considered as one cohort during analysis). Of these, 85 genes were differentially expressed in leiomyo-
mas as compared to peritoneal adhesions (Fig. 2), however exclusion of U133A data from the analysis resulted in identification of a higher number differentially expressed genes. The gene expression profiles in these tissues were comparatively analyzed with their corresponding normal tissues, myometrium, skin and peritoneum, and as expected they displayed distinct patterns (data not shown). The analysis confirmed the effect of cross-platform on gene expression profiling when comparing results of different studies (See Nature Bio-technology, Sept 2006 for several reviews).

Realtime PCR of gene expression
Gene ontology assessment and division into functional categories indicated that a majority of the differentially expressed genes identified in these cohorts serve as regulator of transcription, cell cycle and apoptosis, extracellular matrix turnover, adhesion molecules, signal transduction and transcription factors (Tables 1, 2 and 3). Since the expression of E2F1, RUNX3, EGR3, TBPIP, ECM-2, ESM1, THBS1, GAS1, ADAM17, CST6, FBLN5, and COL18A1 was evaluated in leiomyomas using LDA-based realtime PCR as described in the accompanying manuscript [17] we used the same approach and compared their expression in keloids, incisional scars and peritoneal adhesions. The level of expression of these 12 genes displayed significant variations among these tissues with some overlapping patterns with the microarray results. By setting the mean expression value of each gene independently as 1 in leiomyomas compared with their mean expression in keloids/incisional scars (scar) and adhesions, the results
indicated that the expression of E2F1, TBPIP and ESM1 was elevated in leiomyoma as compared to keloids/incisional scars and adhesions (Fig. 3, \( P < 0.05 \)). In contrast, the expression of EGR3, ECM2, THBS1, GAS1 and FBLN5 in scars and RUNX3 and COL18 expression in peritoneal adhesions was higher as compared to leiomyomas (Fig. 3).

**Discussion**

Using a large-scale gene expression profiling approach we compared leiomyomas with keloids, incisional scars and peritoneal adhesions and found that their molecular environments consist of a combination of both tissue-specific and commonly expressed genes. The tissue-specific gene expression between leiomyomas and keloids was not reflected based on the presence/absence of unique genes, but rather occurred at the level of expression of a selective number of differentially expressed genes. As such an elevated level of expression of a number of muscle cell-specific genes in leiomyomas and fibroblast-specific genes in keloids reflected the specific cellular make up of these tissues. In addition, specific expression of estrogen receptor (ER) in leiomyomas with limited expression in keloids and incisional scar tissues re-enforced the importance of ovarian steroids in leiomyomas growth. Collectively the results suggest that the molecular environments that govern the characteristic of these fibrotic tissues, at least at genomic levels, are relatively similar and involved specific set of genes represented by 3 to 12% of the genes on the array. This observation also suggests that differential expression of a limited number of these genes with unique biological functions may regulate the processes that results in establishment and progression of leiomyoma, keloids, incisional scars, and possibly other fibrotic disorders, despite differences in the nature of their development and growth.

We recognize that the stage of the menstrual cycle and to a limited extend the size of leiomyomas, as well as the period since keloids, incisional scars and peritoneal adhesions were first formed, reflecting the stage of wound healing, influences the outcome of their gene expression. Although leiomyomas used in our study were similar in size and from the same phase of the menstrual cycle, the stage of keloids and scars tissues was unknown. As such the study results represent their gene expression at the time of collection. We also recognize that small sample size limited our ability to analyze the data based on ethnicity, because of more frequent development of leiomyomas and keloids in African Americans. However, it is worth mentioning that comparing leiomyomas with keloids from this ethnic group showed a limited difference in their gene expression profile, or when compared with leiomyomas from Caucasians, suggesting the existence of a comparable environment in leiomyomas and keloids.

![Bar graphs showing gene expression levels](image-url)
Table 2: List of under-expressed in leiomyomas as compared to scar tissues (keloids/incisional scars)

| Gene Bank Symbol | Fold Change | Probability | Function          |
|------------------|-------------|-------------|-------------------|
| MAPK13           | 0.06        | 0.0002      | apoptosis         |
| PTGES            | 0.09        | 0.0003      | apoptosis         |
| CIDEB            | 0.21        | 0.0014      | apoptosis         |
| TRADD            | 0.26        | 0.0007      | apoptosis         |
| CASP1            | 0.31        | 0.0009      | apoptosis         |
| NALP1            | 0.31        | 0.0025      | apoptosis         |
| FRAG1            | 0.33        | 0.0044      | apoptosis         |
| BCL2L1           | 0.42        | 0.0027      | apoptosis         |
| GTSE1            | 0.43        | 0.0033      | apoptosis         |
| LTBR             | 0.50        | 0.0047      | apoptosis         |
| CCND3            | 0.42        | 0.0001      | structural molecule |
| MAP2K3           | 0.22        | 0.0001      | structural molecule |
| DSC2             | 0.01        | 0.0009      | cell adhesion     |
| CDH1             | 0.01        | 0.002       | cell adhesion     |
| SEL              | 0.21        | 0.002      | cell adhesion     |
| ANXA9            | 0.22        | 0.0031      | cell adhesion     |
| PECAM1           | 0.36        | 0.0017      | cell adhesion     |
| KRT14            | 0.26        | 0.0001      | cytokeratin       |
| KRT8B            | 0.005       | 0.0043      | cytokeratin       |
| KRT10            | 0.018       | 0.001      | cytokeratin       |
| COLA3            | 0.14        | 0.00001    | extracellular matrix |
| COL1B1           | 0.49        | 0.0011      | extracellular matrix |
| FGFR3            | 0.007       | 0.0039      | growth factor receptor |
| CXCL14           | 0.009       | 0.0014      | chemokine         |
| TGFα             | 0.2         | 0.0048      | growth factor receptor |
| INHBB            | 0.21        | 0.000001   | cytokine binding  |
| NOV (CCN3)       | 0.28        | 0.0009      | growth factor receptor |
| AGTR1            | 0.30        | 0.005      | growth factor receptor |
| HDGF             | 0.42        | 0.0046      | creatine kinase   |
| MAP2K3           | 0.22        | 0.0048      | protein kinase activity |
| ITPKC            | 0.28        | 0.0036      | protein kinase activity |
| IRAK1            | 0.33        | 0.0001      | protein kinase activity |
| ERBB2            | 0.25        | 0.0003      | protein kinase activity |
| SFN              | 0.001       | 0.0028      | signal transduction |
| HM74             | 0.04        | 0.0047      | signal transduction |
| LTBR4            | 0.06        | 0.0006      | signal transduction |
| EPB1             | 0.12        | 0.0038      | signal transduction |
| EPHB2            | 0.17        | 0.0021      | signal transduction |
| MC1R             | 0.17        | 0.0046      | signal transduction |
| VAV3             | 0.17        | 0.004      | signal transduction |
| GTF2             | 0.2         | 0.0048      | signal transduction |
| CENTD1           | 0.21        | 0.0003      | signal transduction |
| CYB661           | 0.23        | 0.0001      | signal transduction |
| GP56             | 0.23        | 0.0002      | signal transduction |
| CELSR1           | 0.23        | 0.0006      | signal transduction |
| CELSR2           | 0.24        | 0.0003      | signal transduction |
| FZD10            | 0.25        | 0.0009      | signal transduction |
| IPO7             | 0.25        | 0.002      | signal transduction |
| ANX1A2           | 0.27        | 0.0044      | signal transduction |
| THBD             | 0.29        | 0.0004      | signal transduction |
| EFNA1            | 0.31        | 0.0032      | signal transduction |
| HLA-DMB          | 0.33        | 0.0008      | signal transduction |
| TUBB4            | 0.36        | 0.001      | signal transduction |
| GPIR             | 0.4         | 0.0033      | signal transduction |
| TNFRSF5          | 0.4         | 0.0032      | signal transduction |
| EPHB3            | 0.42        | 0.0001      | signal transduction |
| CMKOR1           | 0.46        | 0.0014      | signal transduction |
| IDE              | 0.46        | 0.0031      | signal transduction |
| CENTD2           | 0.47        | 0.0004      | signal transduction |
Further comparison of leiomyomas' gene expression with peritoneal adhesions (Affymetrix U95A subjected to cross-platform comparability analysis) also identified a low number of differentially expressed genes (85 genes) in these tissues, although analysis based only on U95A arrays identified higher numbers. The results indicate that the molecular environment of leiomyomas may be more comparable to peritoneal adhesions as compared to keloids/incisional scars at least at late stage of their wound healing development. Possibly the size of leiomyomas (larger size often undergoing degeneration at the center), and the stage of keloids, incisional scars and adhesions formation following tissue injury influencing their gene expression profiles would produce different results from our study and their evaluation would enhance our understanding of molecular conditions that lead to tissue fibrosis at these and other sites [18-21].

A majority of the genes identified in leiomyomas, keloid, incisional scars and adhesions function as regulators of cell survival (cell cycle and apoptosis), cell and tissue structure (ECM, adhesion molecules and cytoskeleton), tissue turnover, inflammatory mediators, signal transduction and transcription and metabolism. Consistent with the importance of ECM, cytoskeleton, adhesion molecules and proteases in tissue fibrosis we identified the expression of many of genes in these categories some with 5 to 60 fold increase in their expression. Elevated expression of DES, MYH11, MYL9 and SMTN in leiomyomas and several KRTs in keloids and scars reflects the cellular composition of these tissues. Additionally, PALLD has been considered to serve as a novel marker of myofibroblast conversion and is regulated by profibrotic cytokine such as TGF-β [22,23]. SM22, which is overexpressed in keloids[24], promotes ECM accumulation through inhibition of MMP-9 expression [25]. The expression of many components of ECM including collagens, decorin, versican, fibromodulin, intergrins, extracellular matrix protein 1 (ECM-1), syndecan and ESM-1 has been identified in leiomyomas [11,17,26] as well as dermal wounds during healing, scars and keloids (for review see [27-32]).

We validated the expression of ECM-2, ESM1, THBS1, FBLN5...
Table 1: List of over-expressed in leiomyomas as compared to scar tissues (keloids/cesional scars)

| Gene Bank | Symbol | Fold Change | Probability | Function |
|-----------|--------|-------------|-------------|----------|
| NM_003478 | CUL5   | 5.06        | 0.0001      | apoptosis|
| AB037736  | CASP8AP2| 4.07        | 0.0021      | apoptosis|
| NM_018947 | CYCS   | 2.08        | 0.0013      | apoptosis|
| AB014517  | CUL3   | 2.07        | 0.000001    | apoptosis|
| BC010958  | CCND2  | 5.62        | 0.0041      | cell cycle|
| U47413    | CCNG1  | 3.16        | 0.0007      | cell cycle|
| AF048751  | CCL7   | 2.83        | 0.0004      | cell cycle|
| NM_001927 | DBS    | 61.51       | 0.0022      | cytoskeleton/motility|
| AK124338  | ACTG2  | 30.16       | 0.00001     | cytoskeleton/motility|
| BC024015  | CNI    | 27.26       | 0.00001     | cytoskeleton/motility|
| NM_006449 | CDC42EP3| 25.29       | 0.0051      | cytoskeleton/motility|
| AB027209  | KIAA0992| 17.61       | 0.0004      | cytoskeleton/motility|
| AF474156  | TPM1   | 14.84       | 0.0029      | cytoskeleton/motility|
| BC011776  | TPM2   | 12.04       | 0.00001     | cytoskeleton/motility|
| M11315    | COL4A1 | 11.87       | 0.0029      | cytoskeleton/motility|
| AK124747  | LMOD1  | 9.49        | 0.00001     | cytoskeleton/motility|
| AB062484  | CALD1  | 9.22        | 0.0042      | cytoskeleton/motility|
| NM_003186 | TAGLN  | 6.68        | 0.00001     | cytoskeleton/motility|
| BC017554  | ACTA2  | 5.18        | 0.00001     | cytoskeleton/motility|
| AK074048  | FLNa   | 5.08        | 0.00001     | cytoskeleton/motility|
| NM_016274 | CKIP1  | 4.44        | 0.002       | cytoskeleton/motility|
| BC003576  | ACTN1  | 4.23        | 0.0024      | cytoskeleton/motility|
| AF089841  | FLNC   | 3.43        | 0.0005      | cytoskeleton/motility|
| X05610    | COL4A2 | 7.86        | 0.0017      | extracellular matrix|
| BC005159  | COL4A1 | 3.70        | 0.002       | extracellular matrix|
| AB02730   | CAPN6  | 13.7        | 0.0023      | protease activity|
| U41766    | ADAM9  | 4.76        | 0.0021      | protease|
| NM_001110 | ADAM10 | 3.2         | 0.00001     | protease|
| AF031385  | CYR61  | 9.13        | 0.0035      | growth factor|
| M12977    | VEGF   | 7.1         | 0.002       | growth factor|
| AF035287  | SDFR1  | 4.70        | 0.0001      | chemokine receptor|
| X04434    | IGFBP3 | 3.64        | 0.0017      | growth factor receptor|
| AB029156  | FLG    | 5.08        | 0.00001     | growth factor receptor|
| AF056979  | IFNGR1 | 2.72        | 0.0001      | signal transduction|
| AB020673  | MYH11  | 53.80       | 0.0006      | signal transduction|
| D26070    | ITPR1  | 26.18       | 0.0034      | signal transduction|
| AB023117  | SORBS1 | 15.25       | 0.0005      | signal transduction|
| AP110225  | ITGB1BP2| 14.18       | 0.0009      | signal transduction|
| AB004903  | SOCS2  | 11.39       | 0.0002      | signal transduction|
| B011147   | GREB1  | 11.37       | 0.0025      | signal transduction|
| AB000509  | TRAF5  | 7.83        | 0.0032      | signal transduction|
| NM_005261 | GEM    | 7.48        | 0.0003      | signal transduction|
| AF028832  | HSPCA  | 4.27        | 0.00001     | signal transduction|
| AC068681  | MIPR   | 3.85        | 0.0012      | signal transduction|
| AF275719  | HSPCB  | 3.74        | 0.001      | signal transduction|
| AJ242780  | ITPKB  | 3.68        | 0.00001     | signal transduction|
| AK095866  | GPR125 | 3.62        | 0.0001      | signal transduction|
| AF016050  | NRP1   | 3.44        | 0.0011      | signal transduction|
| AB015706  | IL6ST  | 3.42        | 0.0002      | signal transduction|
| AK027120  | HMGB1  | 3.16        | 0.0001      | signal transduction|
| NM_006644 | HSPH1  | 3.14        | 0.002       | signal transduction|
| AB072923  | BSG    | 2.90        | 0.0024      | signal transduction|
| AB010881  | FZD7   | 2.62        | 0.0024      | signal transduction|
| AF273055  | INPP5A | 2.58        | 0.002      | signal transduction|
| AC078943  | TANK   | 2.32        | 0.0005      | signal transduction|
| AF051344  | LTBP4  | 2.20        | 0.0002      | signal transduction|
| A404847   | ILK    | 4.74        | 0.0002      | protein kinase activity|
| AF119911  | CSNK1A1| 3.40        | 0.0015      | protein kinase activity|
| NM_002037 | FYN    | 3.30        | 0.0028      | protein kinase activity|
| AB056894  | CDC2L5 | 2.37        | 0.0001      | protein kinase activity|
| AF415177  | CAMK2G | 2.18        | 0.0008      | protein kinase activity|
| NM_005654 | NRR2F1 | 12.57       | 0.0039      | transcription factor|
| BC062607  | PNN    | 9.93        | 0.0001      | transcription factor|
| AK098174  | MEIS1  | 9.61        | 0.00001     | transcription factor|
| NM_001225 | ESR1   | 9.36        | 0.0004      | transcription factor|
| AF249227  | BCLAF1 | 8.62        | 0.0001      | transcription factor|
| AFO17418  | MEIS2  | 7.46        | 0.0009      | transcription factor|
| AFO45447  | MADH4  | 6.39        | 0.00001     | transcription factor|
and COL18A1 in keloids, incisional scars and adhesions and the analysis indicated an elevated expression of ECM2, THBS1 and FBLN5 in keloid/incisional scars and COL18 in peritoneal adhesions as compared to leiomyomas[17]. Although the biological significance of these gene products and changes in their expression in leiomyomas, keloids and adhesions remains to be established, the product of a specific number of these genes such as ECMS, THBS1, FBLNs, MMPs and ADAMs play a critical role in various aspect of wound healing and tissue fibrosis[27-32]. A number of MMPs were equally expressed in leiomyomas, keloids and peritoneal adhesions with the exception of lower MMP-14, MMP-24 and MMP-28 expression in leiomyomas, suggesting that these tissues are potential target of their proteolytic actions. The biological importance of lower expression of these MMPs in leiomyomas is unknown; however unlike most MMPs that are secreted as inactive proenzymes and require activation, MMP-11 and MMP-28 are secreted in active forms. In keratinocytes, MMP-28 is expressed in response to injury and detected in the conditioned media of hypertrophic scars, but not normotrophic scars[33]. A lower expression of MMP-28 and elevated expression of TIMP-3 in leiomyomas compared to keloids imply a lower matrix turnover with an increase angiogenic and pro-apoptotic activities that has been associated with TIMP-3[34,35].

We identified an overexpression of a higher number of apoptotic-related genes in keloids and incisional scars as compared to leiomyomas, suggesting an increased rate of cellular turnover. Because apoptotic and non-apoptotic cell death is considered to increase local inflammatory reaction and a key step in tissue fibrosis, a number of genes functionally categorized as proinflammatory and pro-fibrotic mediators were identified in these tissues. Noticeable among these genes were TGF-β, IL-1, IL-6, IL-11, IL-13, IL-17, IL-22 and IL-27 and chemokines CCL-2 to 5, CX3CL1, CXCL-1, CXCL-12 and CXCL-14 and their receptors. Elevated expression of PDGF-C, VEGF and FGF2 in leiomyomas as compared to keloids and adhesions imply an additional role for these angiogenic factors in pathogenesis of leiomyomas. While the expression of TGF-β was equally elevated in leiomyomas, keloids, incisional scars and peritoneal adhesion as compared to their

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**Partial list of differentially expressed genes identified in leiomyomas (African Americans and Caucasians) as compared to keloid/incisional scars as shown in Fig. 1. The genes were selected based on p ranking of \( p \leq 0.005 \) and 2-fold cutoff change selection (F. Change) as described in materials and methods. Table 1 displays the over-expressed genes in leiomyomas as compared to keloid/incisional scars.**

| Gene ID | Symbol | Description | F(Change) | p Value |
|---------|--------|-------------|-----------|---------|
| NM_001527 | HDAC2 | Histone deacetylase 2 | 4.76 | 0.0001 |
| NM_004268 | CRSP6 | Connexin 31 | 4.76 | 0.0001 |
| BC020668 | STAT5 | Signal transducer and activator of transcription 5 | 4.57 | 0.0003 |
| BC002646 | JUN | Jun Proto-oncogene | 3.84 | 0.0042 |
| AT342527 | CREB1 | Cyclic AMP Responsive Element Binding Protein 1 | 3.77 | 0.0031 |
| AL931643 | MAX | Max Proto-oncogene | 3.66 | 0.0014 |
| NM_021809 | TGF2 | Transforming growth factor beta 2 | 3.58 | 0.0014 |
| AB007361 | TGFBI1 | Transforming growth factor beta type I receptor | 3.55 | 0.0007 |
| NM_005760 | CEBPZ | CCAAT/enhancer binding protein zeta | 3.53 | 0.0001 |
| AL931268 | MEF2C | Myogenic factor 2C | 3.49 | 0.0019 |
| NM_005903 | MADH5 | Myocyte-specific transcription factor | 3.10 | 0.0037 |
| NM_022739 | SPLR2F | Spleen tyrosine kinase 2 | 2.58 | 0.0013 |
| NM_003472 | DEK | DEK Proto-oncogene | 2.55 | 0.0001 |
| NM_001358 | DDX5 | DEAD (Asp-Glu-Ala-Asp) box polypeptide 5 | 2.49 | 0.0029 |
| BC029619 | ATF1 | Activating transcription factor 1 | 2.41 | 0.0026 |
| AB082525 | TSC2 | Tuberous sclerosis complex 2 | 2.26 | 0.0002 |
| AL931995 | MEF2A | Myogenic factor 2A | 2.25 | 0.0024 |
| AA765467 | DDX17 | DEAD (Asp-Glu-Ala-Asp) box polypeptide 17 | 2.10 | 0.0035 |
| NM_018951 | HOXA1D | Homeobox A1 domain containing | 8.69 | 0.0001 |
| BC000751 | EIF5A | Eukaryotic translation initiation factor 5A | 4.07 | 0.001 |
| AF015812 | DDX5 | DEAD (Asp-Glu-Ala-Asp) box polypeptide 5 | 2.48 | 0.0004 |
| AL099283 | EIF1A | Eukaryotic translation initiation factor 1A | 2.35 | 0.0005 |
| NM_003760 | EIF4G3 | Eukaryotic translation initiation factor 4G3 | 2.35 | 0.0028 |
| NM_012318 | ILF3 | Intracellular signal-regulated kinase 3 | 2.29 | 0.0003 |
| AB001854 | EIF5B | Eukaryotic translation initiation factor 5B | 2.26 | 0.002 |
| AF153908 | HSPB7 | Heat shock protein beta 7 | 9.52 | 0.0002 |
| AF209712 | MCP | Monocyte chemotactic protein | 5.64 | 0.0001 |
| AL933430 | SPARC1 | SPARC like 1 | 5.12 | 0.0004 |
| AF297048 | PTGIS | Prostaglandin I2 synthase | 4.26 | 0.0004 |
| AF298537 | FSTL1 | Fat-storing protein related protein 1 | 4.11 | 0.001 |
| AB034951 | HSPA8 | Heat shock protein A8 | 3.13 | 0.001 |
| NM_001155 | ANXA6 | Annexin A6 | 2.85 | 0.0014 |
| NM_03642 | HAT1 | Heat shock protein 1 | 2.81 | 0.00001 |
| NM_002267 | KIPNA3 | Kinesin related protein A3 | 2.55 | 0.0031 |
| AK124769 | XPO1 | Exportin 1 | 2.46 | 0.0002 |
| AD383428 | CENTB2 | Centromere protein B2 | 2.37 | 0.0045 |
| AF079218 | MTMR6 | Rho GTPase interactive protein 6 | 2.17 | 0.002 |

**Table 1: List of over-expressed in leiomyomas as compared to scar tissues (keloids/incisional scars) (Continued)**
Table 3: Differentially expressed genes in leiomyomas compared to keloids/incesional scars

| Gene Bank Symbol | F. Change LAA:Scar | F. Change LC:Scar | P value | Function                      |
|------------------|--------------------|--------------------|---------|-------------------------------|
| NM_006198        | PCP4               | 68.14              | 6.66    | 0.0017 system development     |
| S6738            | MYOSIN             | 62.78              | 36.69   | 0.0034 cytoskeleton/motility  |
| NM_004342        | Caldi              | 21.43              | 9.32    | 0.0047 cytoskeleton/motility  |
| NM_013437        | LRP12              | 20.6               | 6.82    | 0.0053 cellular process       |
| AC004010         | AMIGO2             | 19.07              | 10.61   | 0.0021 cell adhesion          |
| AF040234         | OCX                | 18.71              | 5.39    | 0.0099 signal transduction    |
| NM_013585        | SORBS1             | 17.44              | 9.26    | 0.0003 cytoskeleton/motility  |
| NM_012878        | ITGB1BP2           | 17.42              | 9.9     | 0.0018 signal transduction    |
| NM_006101        | KNTC2              | 17.33              | 5.23    | 0.0022 transcription factor   |
| NM_001845        | COL4A1             | 16.08              | 5.94    | 0.0029 cytoskeleton/motility  |
| AF104857         | CDC42EP3           | 16.08              | 3.78    | 0.0002 cytoskeleton/motility  |
| AW188131         | DDX17              | 15.65              | 9.11    | 0.0005 translation factor     |
| NM_001057        | TACR2              | 15.6               | 4.51    | 0.0062 signal transduction    |
| AI375002         | ZNF447             | 14.55              | 8.04    | 0.0061 transcription factor   |
| NM_014890        | DOC1               | 14.35              | 5.19    | 0.0002 proteolysis            |
| NM_005781        | VAMP3              | 12.24              | 7.36    | 0.0024 signal transduction    |
| AI1452664        | PNN                | 12.19              | 8.26    | 0.003 transcription factor    |
| NM_003380        | MATN2              | 11.86              | 5.62    | 0.0011 extracellular matrix    |
| NM_007362        | NCBP2              | 11.38              | 8.04    | 0.0034 RNA processing         |
| AK023406         | Macfil             | 8.8                | 4.77    | 0.0041 ECM signaling          |
| AF095192         | BAG2               | 8.01               | 4.34    | 0.0018 apoptosis              |
| NM_001976        | CDKL1              | 7.91               | 2.83    | 0.0017 cell cycle             |
| B512000          | MBNL2              | 7.58               | 3.01    | 0.0014 muscle differentiation |
| AV043713         | Sulf               | 6.9                | 0.78    | 0.0039 hydrolase activity     |
| NM_005781        | VAMP3              | 6.76               | 3.02    | 0.0016 trafficking            |
| AU1452664        | STAT5B             | 5.62               | 3.94    | 0.0043 transcription factor   |
| NM_016277        | RAB23              | 5.61               | 2.68    | 0.0055 signal transduction    |
| AI582238         | TRA1               | 5.13               | 3.46    | 0.0042 calcium ion binding    |
| NM_005722        | ACTR2              | 4.04               | 2.49    | 0.0001 cytoskeleton/motility  |
| AF016005         | RERE               | 4.02               | 2.87    | 0.008 transcription factor    |
| AL046979         | TNS1               | 3.65               | 2.14    | 0.0047 signal transduction    |
| NM_005727        | MBNL2              | 3.57               | 0.84    | 0.0049 muscle development     |
| AI133768         | LDB3               | 3.3                | 1.53    | 0.0056 cytoskeleton/motility  |
| AI680819         | CUL4B              | 3.04               | 1.59    | 0.0045 metabolism             |
| AL013602         | MTK1               | 0.61               | 0.33    | 0.0086 cadmium ion binding    |
| UB5658           | TFP2C              | 0.27               | 0.14    | 0.0083 transcription factor   |
| NM_003790        | TNFRSF25           | 0.19               | 0.11    | 0.007 apoptosis               |
| BC002495         | BAIAp2             | 0.18               | 0.11    | 0.0003 signal transduction    |
| AV691491         | TMEM30B            | 0.13               | 0.09    | 0.0093 cell cycle control     |
| AI689941         | COL4A6             | 10.4               | 30.21   | 0.007 extracellular matrix    |
| AV451711         | PBX1               | 14.44              | 18.14   | 0.0001 transcription factor   |
| NM_014668        | GREB1              | 7.18               | 15.94   | 0.0089 transcription factor   |
| NM_004619        | TRAF5              | 6.47               | 11.46   | 0.0091 signal transduction    |
| NM_004188        | ST5                | 5.83               | 8.1     | 0.0044 signal transduction    |
| BC002811         | SUMO2              | 0.47               | 0.83    | 0.0035 protein binding        |
| AV700891         | ETS2               | 0.28               | 0.54    | 0.0082 transcription factor   |
| AB042557         | PDE4DIP            | 0.2                | 0.39    | 0.0019 signaling              |
| NM_014485        | PGDS               | 0.17               | 0.31    | 0.0027 catalytic activity     |
| AI984221         | COL5A3             | 0.08               | 0.17    | 0.0011 extracellular matrix   |
| NM_006823        | PKIA               | 0.08               | 0.17    | 0.0034 Kinase regulator       |
| AI144294         | IRF6               | 0.04               | 0.15    | 0.0026 transcription factor   |
| NM_000962        | PTGS1              | 0.06               | 0.11    | 0.0046 catalytic activity     |
| NM_0228984       | BCL11B             | 0.05               | 0.09    | 0.0099 transcription factor   |
| NM_001982        | ERBB3              | 0.02               | 0.06    | 0.0066 signal transduction    |
| NM_002705        | PPL                | 0.005              | 0.031   | 0.0073 hydrolase activity     |
| NM_001630        | ANXA8              | 0.006              | 0.02    | 0.0079 calcium ion binding    |
| N74607           | AQP3               | 0.006              | 0.02    | 0.0098 transporter activity   |
| NM_000142        | FGFR3              | 0.007              | 0.009   | 0.01 Growth factor            |

Partial list of differentially expressed genes from several functional categories in leiomyomas from African Americans and Caucasians as compared to keloids/incisional scars as shown in Fig. 2. The genes were selected based on p ranking of p < 0.01 and following 2-fold cutoff change.

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normal tissues reinforcing the importance of TGF-β as principle mediator of tissue fibrosis [30]. Although profibrotic action of TGF-β is reported to involve the induction of CTGF, a member of PDGF family with mitogen action for myofibroblasts [36], it is expressed at lower levels in leiomyomas as compared to myometrium [26,37,38]. However, leiomyomas of African Americans expressed a 3.3 fold higher levels of CTGF as compared to Caucasians, and 12.6 and 4.3 fold higher as compared to keloids and incisional scars, respectively. Although the biological significance of these differences needs further investigation, altered expression of many of these genes as compared to their normal tissues counterpart also imply their potential role in various cellular processes that results in tissue fibrosis.

The genes encoding signal transduction and transcription factors represented the largest functional category in leiomyomas and scar tissues. They included several genes such as NR2F1, PNN, Smad4, Smad5, STAT5B, JUN, TGFβ2, and ATF1 that were over-expressed while RUNX3, STAT1, STAT6, EGR3, GAS7, Smad1, and EDF1 were underexpressed in leiomyomas as compared to keloid/ incisional scars. We validated the expression of E2F1, RUNX3, EGR3 and TBPIP in leiomyomas [17], keloids, incisional scars and peritoneal adhesions showing a good correlation with microarray data. Since activation of these signal transduction pathways and transcription factors regulate the expression of large number of genes with diverse functional activities their altered expression in these tissues could have a considerably more important role in tissue fibrosis than previously considered. Preferential phosphorylation of many of these transcription factors such as Jun, Stats, Smads, Runx and EGRs leads to regulation of target genes involved in cell growth and apoptosis, inflammation, angiogenesis and tissue turnover with central roles in tissue fibrosis [11,17,39-42].

In conclusion, the gene expression profiling involving leiomyomas and their comparison with keloids, incisional scars and peritoneal adhesions indicated that a combination of tissue-specific and common genes differentiate their molecular environments. The tissue-specific differences were not based on the presence/absence of unique genes, but rather the level of expression of selective number of genes accounting for 3 to 12% of the genes on the array. Although the nature of leiomyomas' development and growth is vastly different from these fibrotic tissues, we speculate that the outcome of their tissue characteristics is influenced by the products of genes regulating cell growth and apoptosis, inflammation, angiogenesis and tissue turnover, and may also be under different tissue-specific regulatory control.

Competing interests
The author(s) declare that they have no competing interests.

Authors’ contributions
XL, QP and NC participated in all aspects of the experimental design and writing of the work presented here. The final microarray gene chips were performed at Interdisciplinary Center for Biotechnology Research at the University of Florida. The analysis of microarray gene expression profiles between the gene chips U95 and 133a was carried out by LL and gene expression analysis and realtime PCR was performed by XL and QP. All the authors read and approved the final manuscript.

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