ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 9, Issue, 1(I), pp. 23463-23469, January, 2018

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

PROTEOMICS AND UTERINE LEIOMYOMAS: A NARRATIVE REVIEW FOR BETTER UNDERSTANDING OF THE DISEASE

Shadab Anjum., Tahreem Sahar., Shafaque Imran and *Saima Wajid

Department of Biotechnology, School of Chemical and Life Sciences,
Jamia Hamdard, New Delhi, India

DOI: http://dx.doi.org/10.24327/ijrsr.2018.0901.1474

ARTICLE INFO

Article History:

Received 15th October, 2017
Received in revised form 25th October, 2017
Accepted 23rd December, 2017
Published online 28th January, 2018

Key Words:

Uterine leiomyoma/fibroid, proteomics, tumor

ABSTRACT

Uterine leiomyomas are monoclonal benign tumors affecting a major proportion of the reproductively active female population. Despite its high occurrence rate, the understanding of the etiology and the molecular mechanism involving disease progression still remains poorly understood. Proteomics allows the identification of thousands of proteins inside the cell and simultaneous observation of any alteration in the protein expression which has, if any, impact on its clinical manifestation. As we know that proteins are the real time players of the cell hence, proteomics can provide a better understanding of the physiology of disease. Use of proteomics in uterine leiomyomas research might help to identify myoma specific proteins, disease pathway and importantly the potential biomarkers for early detection.

INTRODUCTION

Uterine Leiomyomas (also known as fibroids) are the monoclonal tumors originating from the smooth muscle cells of the myometrium and are generally benign in nature (Linder and Gartler, 1965). These are the most common benign pelvic tumor affecting nearly 70% of women in their reproductive age and despite 70% of women may have UL, 20-30% of women are symptomatic, that is, may have abnormal uterine bleeding or pelvic pain. These monoclonal fibroids are characterized by the excess of the extracellular matrix (Moroni *et al*., 2014). Since there are very few deaths associated with fibroids, hence these are generally associated with morbidity rather than mortality. Hysterectomy and Myomectomy are one of the leading gynecological surgical operations in the United States (Cardozo *et al*., 2012). Based on their location in the uterus, leiomyomas are classified into 4 primary types which include subserous, intramural, submucous and pedunculated type (McLucas, 2008). The size of the tumor may vary from 10mm to 20cm. It has been observed that in most of the cases there is generally more than one fibroid in the uterus (Walker and Stewart, 2005). The normal function of the uterus is disrupted leading to several complications like heavy menstrual bleeding, iron deficiency (anemia), pelvic discomfort and complications in pregnancy. There is generally no any visible symptom in patients with fibroids and hence, fibroid size and location are the critical determinants of its clinical manifestation.

The etiology of leiomyomas is still not completely understood and they are believed to grow under the influence of steroid hormones. As uterine leiomyoma is associated with steroid hormones and hence these hormones can be used as identifying factor as they rarely appear before menarche, the growth of fibroid is mainly during reproductive years and it regresses after menopause. In addition to the steroid hormones, other factors like growth factors and cytokines also contribute to the pathophysiology of the leiomyomas. The other risk factors identified with leiomyomas include obesity, ethnicity, and a positive family history (Flake *et al*., 2003). The increase in adipose tissue is linked to increased estrogen production (Tanko *et al*., 2004). The level of free circulating estrogen is increased in obesity, as obesity decreases the hepatic production of sex hormone binding globulin. The race also plays an important role in etiology of fibroids. It has been found that the risk of having leiomyoma is 2-3 times higher in African-American than Caucasian population (Marshall *et al*., 1997). This review summarizes different proteins involved (identified in previous studies that have specific roles in the growth and development of leiomyomas) and the proteomic tools used for the analysis and study of these proteins.

Corresponding author:* **Saima Wajid
Department of Biotechnology, School of Chemical and Life Sciences, Jamia Hamdard, New Delhi, India

Molecular Epidemiology and Pathways

As the molecular basis of uterine fibroid is poorly understood, there are several pathogenic factors such as genetic, growth factors, cytokines, chemokines, microRNA, steroids and extracellular matrix components that contribute to the growth and development of this disease.

Estrogen and progesterone are the main steroid hormones that are known through various studies to promote growth and development of leiomyomas. The growth promoting effect on myomas by estrogen and progesterone is due to the expression of growth factors, cytokines, apoptotic factors and extracellular matrix (Grings *et al*., 2012). Various signaling pathways are activated by estrogen which upregulates expression of PDGF, TGFβ, IGF-1, EGFR and promotes growth and survival by down regulating p53. Progesterone through its receptor exerts mitogenic activity by up-regulating EGF, TGFβ, Bcl-2 and down-regulating TNF-α (Ishikawa *et al*., 2010; Maruo *et al*., 2000). Growth factors are the molecule that regulates cell growth, proliferation, and differentiation.

There are a number of growth factors like EGF, PDGF, TGFβ, bFGF which along with its receptors have been reported to play an important role in the growth of leiomyomas (Ciavattini *et al*., 2013). A number of these factors are upregulated and their upregulation promotes mitogenesis (TGFβ, EGF, PDGF, and IGF), expression of various ECM components (TGFβ), increased DNA synthesis (EGF & PDGF) or smooth muscle cell proliferation and differentiation (IGF). Angiogenesis is considered to be an essential part of tumor growth and survival and is regulated by various angiogenic and growth factors. It has been found that βFGF is a potential inducer of angiogenesis and has increased expression in leiomyoma as compared to myometrium (Dixon *et al*., 2002). Fibulin-3 another important factor that has an antagonist effect on the angiogenesis in tumors and has been reported to be significantly down regulated in leiomyomas and is found to be associated with increased tumor angiogenesis (Albig *et al*., 2006). Activin-A and myostatin have recently been found to be highly expressed in leiomyomas as compared to myometrium.

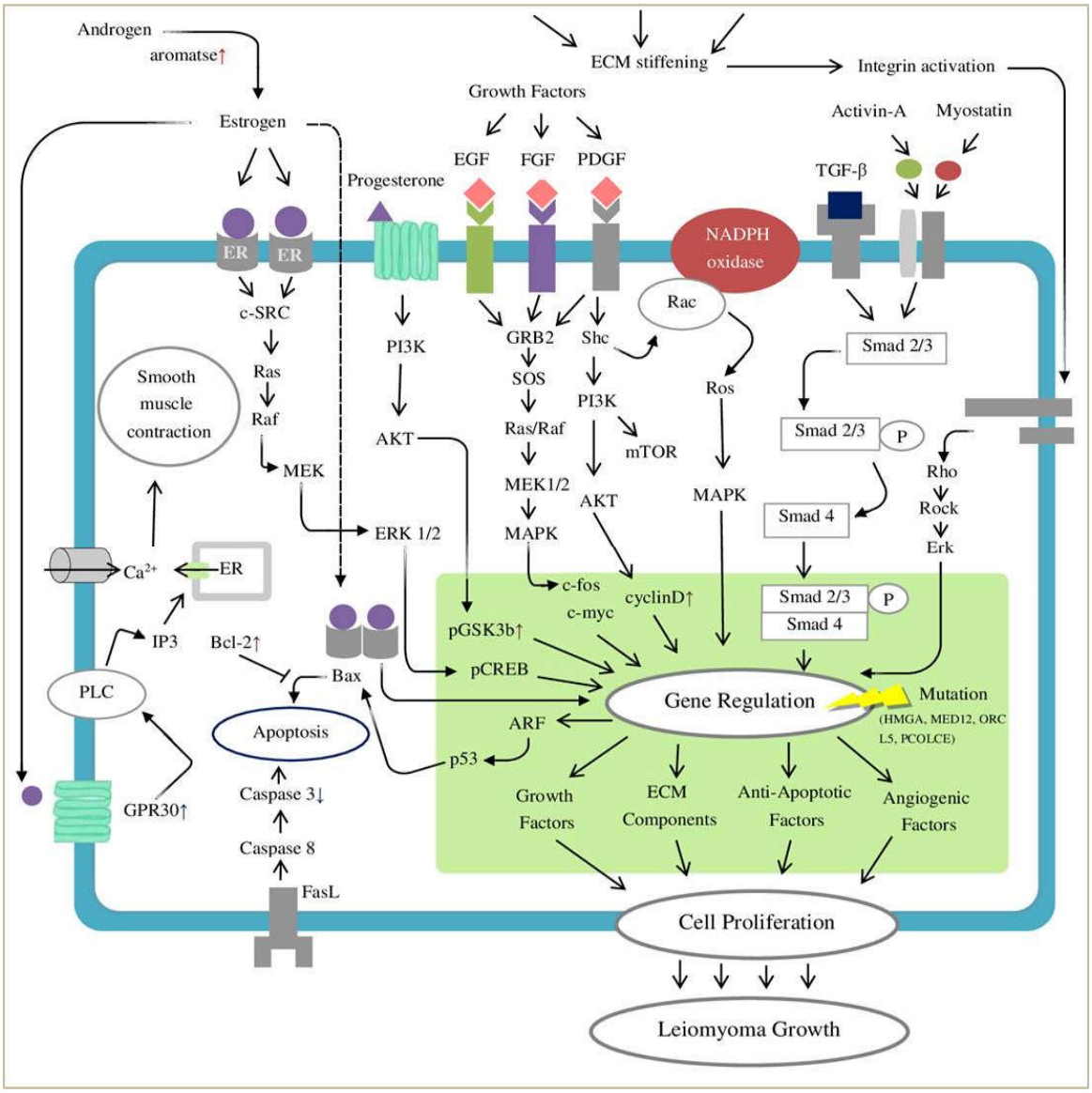

Figure 1 A schematic representation showing the molecular mechanism involved in Uterine Leiomyoma growth and development. Various growth factors are shown to be interacting with their ligands and in turn resulting in activating multiple signaling pathways found to be involved in the leiomyoma growth and development. (This figure has been adopted from kegg and through various literatures and designed based on it).

Activin-A plays role in the expression of various ECM components like fibronectin, collagen1-A1, and versican whereas, the role of myostatin has been shown to be directly associated with the intensity of dysmenorrhea and activates both Smad2/3 signaling pathway (Islam *et al*., 2014; Tsigkou *et al*., 2015). Some studies have come up reporting that abnormal uterine contraction which might play a role in the pathogenesis of uterine leiomyomas (Nishino *et al*., 2005). Calcium ions are important molecules that initiate cell contraction. High expression of calcium channel protein TRPC1 & TRPM7 in leiomyomas regulates intracellular Ca^{2+} homeostasis than myometrium which has a role in leiomyomas cell proliferation (Ke *et al*., 2014). The overall decrease in apoptosis is also one of the factors that contribute to the tumor growth and development. Molecules of both intrinsic and extrinsic apoptotic pathway have shown to be altered in leiomyomas. Bcl-2 protein, an apoptotic protein of intrinsic pathway was reported to be up-regulated in leiomyomas. Its enhanced expression was due to the progesterone while its down-regulation was because of estrogen (Matsuo *et al*., 1997). In another study, caspase-3, a protein having the central role in the extrinsic pathway of apoptosis, decreased in the leiomyoma whereas the level of ki-67 antigen, a nuclear protein necessary for cellular proliferation was found to increase (Plewka *et al*., 2011). sFRP1(secreted frizzled-related protein 1), also an anti-apoptotic protein is upregulated in leiomyomas under the control of estrogen and hence might contribute to the pathogenesis of the disease (Fukuhara *et al*., 2002). Figure 1 shows the molecular mechanism involved in Leiomyoma growth and development and the multiple signaling pathways involved in the leiomyoma growth and development. Estrogens activates the expression of various growth factors, ECM components, cytokines and apoptotic factors as well as through interaction of GPR30 regulates intracellular Ca^{2+} homeostasis which causes abnormal uterine contraction and thus contributes to the leiomyoma growth and development. TGF-β, activin-a, & myostatin contributes to leiomyoma growth through the activation of common Smad 3/4 signalling pathway. The factors like infection, oxidative stress and tissue injury activates the fibroblast that induces tissue stiffening. This causes mechanical stress and activates the integrins which further activates the Rho/ROCK pathway and induces leiomyoma growth. FGF have been shown to promote angiogenesis in leiomyomas cell whereas PDGF & EGF have been reported to increase DNA synthesis through the activation of kinase pathway and also modulates the rate of cell proliferation in leiomyomas cell. Progesterone sensitivity increased due to the increase in the levels of progesterone receptors by estrogens leads to the activation of AKT pathway that induces cell proliferation, inhibiting apoptosis through increasing the expression of various growth factors, ECM components & antiapoptotic factors like Bcl-2.

Extracellular matrix plays a vital role in the growth and development of leiomyomas. It is found that there is an excess production of extracellular matrix proteins which includes collagen type I & III, proteoglycans and matrix metalloproteinases (MMP) (Malik *et al*., 2010). The collagen fibrils present in the fibroids are short and disordered and the ratio of type I/III collagen fibrils is also altered (Leppert *et al*., 2004). MMP are known to play roles in degrading both matrix and non-matrix proteins that are important for tissue repair and remodeling. Other roles played by MMP's are in cell growth, differentiation, migration, apoptosis and inflammatory responses and its action are controlled by tissue inhibitor of MMPs (TIMPs). The MMPS and TIMPs are differentially expressed in leiomyomas. Changes in the ECM affect the mechanical stress and activate the internal signaling that results in cell proliferation (Islam *et al*., 2013). Leiomyoma growth and regression due to tissue remodeling involving extracellular matrix turnover are regulated by the action of both matrix metalloproteinases (MMPs) and the tissue inhibitor of MMPs (TIMPs). Studies have reported that leiomyomas express MMP and TIMP and their expression suggested their hormonal regulation. One study has reported that increase in MMP and reduction in TIMP expression favored extracellular matrix degradation which resulted in the reduction in leiomyoma size because of GnRH-a (Dou *et al*., 1997). Versican is an important proteoglycan that interacts with other proteins and modulates the organization of the ECM and promotes leiomyoma growth and cellular proliferation. It was reported that versican variants V0 and V1 were over-expressed in leiomyomas and their expression was regulated by TGF-β. It has been reported that increased expression of versican variants in leiomyomas may lead to both disorganization of the ECM and increased stiffness of these tumors (Norian *et al*., 2009). It can thus be concluded that the role of extracellular matrix in myoma biology and their abnormal production and accumulation may lead to increased cellular proliferation which can significantly contribute to tumor growth.

Genetic Factors

It has been shown that approximately 50% of the fibroids show cytogenetic abnormalities (Barbieri *et al*., 1991). These chromosomal abnormalities include transversion, deletion, rearrangement and trisomy 12 (Ligon and Morton, 2000). HMGA1 & HMGA2 are the architectural transcription factor encoding high mobility group protein which regulates the transcription of various genes. Chromosomal translocation is found in HMGA1 at 6p21 & HMGA2 at 12q15 and these alterations generally result in up-regulation of their expression that has been associated with large tumor size which indicates its potential role in promoting tumor growth (Pedeutour *et al*., 2000; Peng *et al*., 2008). Mediator complex subunit 12 gene (MED-12) was found to be highly mutated in uterine leiomyomas as identified by exome sequence analysis and was in the region of exon-2 (Mäkinen *et al*., 2011). Mutation in MED12 resulted in the dissociation of Cyclin C-CDK 8 from the core mediator complex and thus affected mediator associated kinase activity (Turunen *et al*., 2014).

Proteomics-Definition and Techniques

Proteins are a dynamic entity that varies with time and different stresses and responds to it. Proteomics is an approach that allows the global study of proteins to understand their expression patterns and the interaction taking place between them. Proteomics research has been categorized into two-Expression proteomics and Cell mapping proteomics (Blackstock and Weir, 1999). A new field of disease proteomics has emerged which initiated from the expression proteomics and involves the comparative study for the analysis of differentially expressed proteins that can be used as molecular targets for the therapeutic and diagnostic purposes

(Hanash, 2003). Several technologies have been developed in this field and have been categorized into two groups: Gel-based separation techniques and non-gel based separation techniques. Gel based separation technique is the primary technique used which involves 1D electrophoresis which separates proteins on the basis of molecular weight & 2D gel electrophoresis and has been used for the separation of proteins first on the basis of their pH and then on the basis of their molecular weight (Adams and Gallagher, 2004). However, because of some disadvantages like low reproducibility rate, protein loss during electrophoresis and the requirement of a large amount of sample, some advancement have been made in these techniques such as the introduction of the immobilized pH gradient (IPG) and the differential gel electrophoresis (DIGE) to overcome these problems. The use of IPG strips resulted in the high resolution and better reproducibility rate whereas 2D-DIGE minimized gel to gel variations and the use of a fluorescent dye for the comparison of proteins can detect nanogram of labeled proteins for protein comparison (Görg *et al*., 2009; Ünlü *et al*., 1997). Despite the fact that even after the advancements in the 2D electrophoresis, it still remains to be non-automated for high throughput analysis. A number of non-gel based separation techniques have been developed to overcome the drawbacks associated with the gel-based techniques. These techniques either involve the labeling of proteins or can be label free. LC has become one of the most commonly used technique and is combined with mass spectrometry for the analysis of proteins. Isotope-coded affinity tag (ICAT) is a quantitative method for the analysis of a complex mixture of proteins using chemical isotope labeling reagents (Gygi *et al*., 1999). This technique involves the labeling of proteins in the sample with heavy or light ICAT reagents followed by digestion with trypsin. The mixture is then separated through chromatographic techniques and the resulting peptides are analyzed using mass spectrometry. Multidimensional Protein Identification Technology (Mud PIT) is another gel free approach for the analysis of proteins (Kline and Wu, 2009). This approach involves the combination of two chromatographic techniques: strong cation exchange and reverse phase. The proteins are first digested by trypsin to give peptide components that are then subjected to the chromatographic system and separated by strong cation exchange (SCX) and reverse phase HPLC, then the peptide components enter mass spectrometer from the reverse phase column and are analyzed using different databases (Wolters *et al*., 2001). MS has also been employed for direct profiling or imaging of proteins present in the tissue section and the use of protein array technology is an important development that initiated nonseparation based techniques for proteome analysis.

Proteomics and Uterine Fibroids

A lot of studies have been done using proteomic techniques to identify differentially expressed in leiomyomas and its comparison with the adjacent myometrium. A group utilized both cDNA microarray and 2D-GE to study the genes and proteins involved in the pathophysiology of leiomyomas. They reported 33 protein spots that are consistently differentially regulated. Of these spots, 17 proteins were found to be upregulated, a majority of which belonged to the nucleic acid binding activity, signal transducer and transporter activity and 16 proteins were down-regulated and belonged to the category of cell adhesion activity, cell motility, muscle development, actin cytoskeleton activity & motor activity. It was found through the use of 2D-PAGE combined with mass spectrometry that mimecan and 14-3-3β were differentially expressed and 14-3-3β expression was higher in African American's than Caucasian's. An isoform of 14-3-3 protein called 14-3-3γ was found to be downregulated in leiomyoma tissues by using LC-MS technology (Lv *et al*., 2008). While another group have used LC-MS/MS for identifying proteomic features associated with this tumor and through this study have concluded that there is an over-expression of extracellular matrix components, estrogen and progesterone receptors in uterine leiomyomas, and has proposed biological pathways leading to the pathophysiology of this tumor (Rizzello *et al*., 2017).

Further study using microarray and 2D-GE showed that some proteins were differentially expressed in leiomyomas like dermatopontin, keratin-19 and IGF-1 proteins were downregulated and some were upregulated like tomoregulin and aromatase P450. Dermatopontin is an ECM protein which interacts with decorin and TGFβ, and promotes cellular adhesion and accelerates assembly of collagen into fibrils. The decrease in the level of dermatopontin expression might possibly result in abnormal collagen fiber formation resulting in altered ECM which ultimately leads to leiomyoma phenotype. Keratin 19 is intermediate filament proteins responsible for the structural integrity of epithelial cells. It has been reported to be down regulated in several cancerous tumors such as squamous cell carcinoma where it is involved in increasing invasive potential. Tomoregulin upregulates cancer cell proliferation by promoting ERK 1/2 phosphorylation and aromatase is involved in the conversion of androgens into estrogen. Ethnicity is considered amongst one of the factors playing role in leiomyoma (Zhu *et al*., 2006).

Apart from the analysis of proteins present in the tissue sample, proteomics-based studies have been done on different samples. A study for quantitative analysis was performed to identify the leiomyoma associated plasma proteins using 2D-DIGE combined with MALDI-TOF-MS. They identified 13 unique plasma proteins majority of which belonged to the category of transportation and coagulation. Carbonic anhydrase 1 belongs to the family of metalloenzyme that catalyzes the hydration of CO2 and maintains acid-base balance. Furthermore, they validated two other proteins, leucine-rich alpha-2-glycoprotein, and vitamin D binding protein, using immunoblot and ELISA analysis and these can be used as a potential biomarker for the diagnosis of leiomyomas (Lin *et al*., 2012). A different study reported that Leucine-rich alpha-2 glycoprotein was upregulated from the analyzed peritoneal fluid of women with leiomyomas using 2DE and LC-MS/MS analysis (Ferrero *et al*., 2009). However, out of six isoforms, only one isoform LRGm had enhanced expression that might be involved in the pathogenesis of leiomyomas through the interaction with TGF-β. Another sample used for proteomics analysis was the interstitial fluid of leiomyomas. It not only consists of plasma proteins but also a large number of abnormal proteins secreted by the tumor cells. The analysis of interstitial fluid revealed 14 protein to be differentially expressed in leiomyomas in which 3 spots were found to be upregulated that included α1-antitrypsin, desmin & peroxiredoxin-2 whereas 11 proteins were down-regulated that were prelamin A/C, transgelin, α-actinin-1 & hsp70 1A/1B (Ura *et al*., 2015). Table 1 gives a

view of different proteomic methods used to identify different proteins in uterine leiomyoma.

Table 1 Proteins identified by the previous studies that applied proteomic approach

Reference	Sample size	Technique	Result
Ahn *et al*. (2003)	n=6; intramural Leiomyoma and the matched myometrium	2D-GE, RT-PCR, cDNA microarray	17 spots (↑) 16 spots (↓)
Zhu *et al*. (2006)	n=17; leiomyoma and the matched myometrium	2D-GE	Dermatopontin (↓), keratin 19 (↓), IGF-1 (↓), tomoregulin (↑)
Pan *et al*. (2007)	n=6; 3-Caucasian & 3-African American; Subserosal/Intramural; myoma & matched myometrium	Microarray, RT-PCR, 2D-GE, MS, Western blot	Keratins, annexin A1 &V, transgelin, mimecan, 14-3-3 isoforms, retinoic acid binding protein, mimecan, 14-3-3β
Jieqiang *et al*. (2007)	n=10; leiomyoma & matched myometrium	2D-GE, LC-MS, RT-PCR, Western blot	14-3-3γ (↓)
Ferrero *et al.* (2008)	n=14; leiomyoma patients & n=14 without leiomyoma Intramural/subserosal	2D-GE, LC-MS/MS	Leucine rich alpha 2 glycoprotein (LRGm)
Lin *et al*. (2011)	n=5 leiomyoma patients & n=8 healthy donors	2D-DIGE MALDI-TOF-MS ELISA	Vitamin D, Carbonic anhydrase, leucine-rich alpha-2-Glycoprotein
Lemeer *et al*. (2015)	n=8; myoma and the matched myometrium	SDS-PAGE LC-MS/MS	DDR1 (↑) CDK5 (↑) Desmin (↑),
Ura *et al.* (2015)	n=10; interstitial fluid of leiomyoma and matched myometrium	2D-GE, MALDI-TOF/TOF MS	α1 antitrypsin (↑), peroxiredoxin-2 (↑) hsp70 1A/1B (↓), α-actinin-1 (↓), Perlamin-A/C (↓), Transgenin (↓)

FUTURE PERSPECTIVE & CONCLUSION

Despite being benign in origin, fibroids are associated with significant morbidity in almost 75 % of the reproductive age women and most of them have to undergo myomectomy or hysterectomy to remove those fibroids. The cost of surgical operation is high and affects a lot to the poor people. Because of its high prevalence rate, it is essential to understand the exact etiology of the disease. There has been much research done on the genetic cause of the disease pathogenesis, however as proteins are the real time players of the cell and the alteration in proteins in diseased tissue can`t be solely predicted from the genomic analysis. For example, a study by Ura *et al* in 2015 revealed altered protein expression in uterine leiomyoma. In this study, two-dimensional gel electrophoresis and mass spectrometry were used to generate and compare the global profiles of interstitial fluid in leiomyoma with that of normal tissue. On comparing the interstitial fluid profile of leiomyoma with that of the normal myometrium, the levels of seven proteins were found to be significantly regulated. The upregulated proteins were desmin, α1-antitrypsin, and peroxiredoxin while the levels of prelamin-A/C, transgelin, hsp70 1A/1B and α-actinin-1 were downregulated. Therefore, looking at these proteomic data we can say that disease-related application of proteomics can provide the better understanding of the pathogenesis of leiomyomas. As genomics doesn't give information about post-translation modifications, advancement in proteomic technologies would be useful for studying disease-specific protein expression patterns that can be further used for diagnostic and therapeutic purposes in uterine fibroids.

Conflict of Interest

Authors declare no conflict of interest.

References

Adams LD, Gallagher SR. (2004). Two-dimensional gel electrophoresis. Current Protocols in Molecular Biology:10.4. 1-10.4. 23.

Albig AR, Neil JR, Schiemann WP. (2006). Fibulins 3 and 5 antagonize tumor angiogenesis in vivo. Cancer Research 66:2621-2629.

Barbieri RL, Friedman AJ, Pavelka K, Fletcher JA, Morton CC, Rein MS. (1991). Cytogenetic abnormalities in uterine leiomyomata. Obstetrics & Gynecology 77:923-926.

Blackstock WP, Weir MP. (1999). Proteomics: quantitative and physical mapping of cellular proteins. Trends in biotechnology 17:121-127.

Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. (2012). The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol 206:211.e1-9.

Ciavattini A, Di Giuseppe J, Stortoni P, Montik N, Giannubilo SR, Litta P, Islam MS, Tranquilli AL, Reis FM, Ciarmela P. (2013). Uterine fibroids: pathogenesis and interactions with endometrium and endomyometrial junction. Obstetrics and gynecology international 2013.

Dixon D, Flake GP, Moore AB, He H, Haseman JK, Risinger JI, Lancaster JM, Berchuck A, Barrett CJ, Robboy SJ. (2002). Cell proliferation and apoptosis in human uterine leiomyomas and myometria. Virchows Archiv 441:53-62.

Dou Q, Tarnuzzer RW, Williams RS, Schultz GS, Chegini N. (1997). Differential expression of matrix metalloproteinases and their tissue inhibitors in leiomyomata: a mechanism for gonadotrophin releasing hormone agonist-induced tumour regression. Molecular human reproduction 3:1005-1014.

Ferrero S, Gillott DJ, Remorgida V, Anserini P, Ragni N, Grudzinskas JG. (2009). Increased expression of one isoform of leucine-rich alpha-2-glycoprotein in peritoneal fluid of women with uterine leiomyomas. Archives of gynecology and obstetrics 279:365-371.

Flake GP, Andersen J, Dixon D. (2003). Etiology and pathogenesis of uterine leiomyomas: a review. Environmental health perspectives 111:1037.

Fukuhara K, Kariya M, Kita M, Shime H, Kanamori T, Kosaka C, Orii A, Fujita J, Fujii S. (2002). Secreted frizzled related protein 1 is overexpressed in uterine leiomyomas, associated with a high estrogenic environment and unrelated to proliferative activity. The Journal of Clinical Endocrinology & Metabolism 87:1729-1736.

Görg A, Drews O, Lück C, Weiland F, Weiss W. (2009). 2-DE with IPGs. Electrophoresis 30.

Grings AO, Lora V, Ferreira GD, Brum IS, Corleta H, Capp E. (2012). Protein expression of estrogen receptors alpha and beta and aromatase in myometrium and uterine leiomyoma. Gynecol Obstet Invest 73:113-7.

Gygi SP, Rist B, Gerber SA, Turecek F, Gelb MH, Aebersold R. (1999). Quantitative analysis of complex protein mixtures using isotope-coded affinity tags. Nature biotechnology 17:994-999.

Hanash S. (2003). Disease proteomics. Nature 422:226-232.

Ishikawa H, Ishi K, Serna VA, Kakazu R, Bulun SE, Kurita T. (2010). Progesterone is essential for maintenance and growth of uterine leiomyoma. Endocrinology 151:2433-42.

Islam MS, Protic O, Stortoni P, Grechi G, Lamanna P, Petraglia F, Castellucci M, Ciarmela P. (2013). Complex networks of multiple factors in the pathogenesis of uterine leiomyoma. Fertil Steril 100:178-93.

Islam SS, Mokhtari RB, El Hout Y, Azadi M, Alauddin M, Yeger H, Farhat WA. (2014). TGF-β1 induces EMT reprogramming of porcine bladder urothelial cells into collagen producing fibroblasts-like cells in a Smad2/Smad3-dependent manner. Journal of cell communication and signaling 8:39-58.

Ke X, Cheng Z, Qu X, Dai H, Zhang W, Chen Z-J. (2014). High expression of calcium channel subtypes in uterine fibroid of patients. International journal of clinical and experimental medicine 7:1324.

Kline KG, Wu CC. (2009). MudPIT analysis: application to human heart tissue. Membrane Proteomics: Methods and Protocols:281-293.

Leppert PC, Baginski T, Prupas C, Catherino WH, Pletcher S, Segars JH. (2004). Comparative ultrastructure of collagen fibrils in uterine leiomyomas and normal myometrium. Fertility and sterility 82:1182-1187.

Ligon AH, Morton CC. (2000). Genetics of uterine leiomyomata. Genes, Chromosomes and Cancer 28:235-245.

Lin C-P, Chen Y-W, Liu W-H, Chou H-C, Chang Y-P, Lin S-T, Li J-M, Jian S-F, Lee Y-R, Chan H-L. (2012). Proteomic identification of plasma biomarkers in uterine leiomyoma. Molecular BioSystems 8:1136-1145.

Linder D, Gartler SM. (1965). Glucose-6-phosphate dehydrogenase mosaicism: utilization as a cell marker in the study of leiomyomas. Science 150:67-69.

Lv J, Zhu X, Dong K, Lin Y, Hu Y, Zhu C. (2008). Reduced expression of 14-3-3 gamma in uterine leiomyoma as identified by proteomics. Fertility and sterility 90:1892-1898.

Mäkinen N, Mehine M, Tolvanen J, Kaasinen E, Li Y, Lehtonen HJ, Gentile M, Yan J, Enge M, Taipale M. (2011). MED12, the mediator complex subunit 12 gene, is mutated at high frequency in uterine leiomyomas. Science 334:252-255.

Malik M, Norian J, McCarthy-Keith D, Britten J, Catherino WH. (2010). Why leiomyomas are called fibroids: the central role of extracellular matrix in symptomatic women. Semin Reprod Med 28:169-79.

Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA, Willett WC, Hunter DJ. (1997). Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstet Gynecol 90:967-73.

Maruo T, Matsuo H, Samoto T, Shimomura Y, Kurachi O, Gao Z, Wang Y, Spitz IM, Johansson E. (2000). Effects of progesterone on uterine leiomyoma growth and apoptosis. Steroids 65:585-92.

Matsuo H, Maruo T, Samoto T. (1997). Increased expression of Bcl-2 protein in human uterine leiomyoma and its up-regulation by progesterone. The Journal of Clinical Endocrinology & Metabolism 82:293-299.

McLucas B. (2008). Diagnosis, imaging and anatomical classification of uterine fibroids. Best Pract Res Clin Obstet Gynaecol 22:627-42.

Moroni R, Vieira C, Ferriani R, CandidodosReis F, Brito L. (2014). Pharmacological treatment of uterine fibroids. Annals of medical and health sciences research 4:185-192.

Nishino M, Togashi K, Nakai A, Hayakawa K, Kanao S, Iwasaku K, Fujii S. (2005). Uterine contractions evaluated on cine MR imaging in patients with uterine leiomyomas. European journal of radiology 53:142-146.

Norian JM, Malik M, Parker CY, Joseph D, Leppert PC, Segars JH, Catherino WH. (2009). Transforming growth factor β3 regulates the versican variants in the extracellular matrix-rich uterine leiomyomas. Reproductive sciences 16:1153-1164.

Pedeutour F, Quade BJ, Sornberger K, Tallini G, Ligon AH, Weremowicz S, Morton CC. (2000). Dysregulation of HMGIC in a uterine lipoleiomyoma with a complex rearrangement including chromosomes 7, 12, and 14. Genes, Chromosomes and Cancer 27:209-215.

Peng Y, Laser J, Shi G, Mittal K, Melamed J, Lee P, Wei J-J. (2008). Antiproliferative effects by Let-7 repression of high-mobility group A2 in uterine leiomyoma. Molecular Cancer Research 6:663-673.

Plewka A, Plewka D, Madej P, Nowaczyk G, Sieron-Stoltny K, Jakubiec-Bartnik B. (2011). Processes of apoptosis and cell proliferation in uterine myomas originating from reproductive and perimenopausal women. Folia Histochemica et Cytobiologica 49:398-404.

Rizzello A, Franck J, Pellegrino M, De Nuccio F, Simeone P, Fiore G, Di Tommaso S, Malvasi A, Tinelli A, Fournier I. (2017). A Proteomic Analysis of Human Uterine Myoma. Current Protein and Peptide Science 18:167-174.

Tanko LB, Bruun JM, Alexandersen P, Bagger YZ, Richelsen B, Christiansen C, Larsen PJ. (2004). Novel associations between bioavailable estradiol and adipokines in elderly women with different phenotypes of obesity: implications for atherogenesis. Circulation 110:2246-52.

Tsigkou A, Reis FM, Ciarmela P, Lee MH, Jiang B, Tosti C, Shen F-R, Shi Z, Chen Y-G, Petraglia F. (2015). Expression levels of myostatin and matrix metalloproteinase 14 mRNAs in uterine leiomyoma are correlated with dysmenorrhea. Reproductive Sciences 22:1597-1602.

Turunen M, Spaeth JM, Keskitalo S, Park MJ, Kivioja T, Clark AD, Mäkinen N, Gao F, Palin K, Nurkkala H. (2014). Uterine leiomyoma-linked MED12 mutations disrupt mediator-associated CDK activity. Cell reports 7:654-660.

Ünlü M, Morgan ME, Minden JS. (1997). Difference gel electrophoresis. A single gel method for detecting changes in protein extracts. Electrophoresis 18:2071-2077.

Ura B, Scrimin F, Zanconati F, Arrigoni G, Monasta L, Romano A, Banco R, Zweyer M, Milani D, Ricci G. (2015). Two-dimensional gel electrophoresis analysis of the leiomyoma interstitial fluid reveals altered protein expression with a possible involvement in pathogenesis. Oncology reports 33:2219-2226.

Walker CL, Stewart EA. (2005). Uterine fibroids: the elephant in the room. Science 308:1589-92.

Wolters DA, Washburn MP, Yates JR. (2001). An automated multidimensional protein identification technology for shotgun proteomics. Analytical chemistry 73:5683-5690.

Zhu X-q, Zhu C-d, Lü J-q, Dong K. (2006). Identification of differential proteins in uterine leiomyoma by two-dimensional electrophoresis. Chinese Journal of Cancer Research 18:203-208.

How to cite this article:

Shadab Anjum *et al.*2018, Proteomics And Uterine Leiomyomas: A Narrative Review For Better Understanding of The Disease. *Int J Recent Sci Res.* 9(1), pp. 23463-23469. DOI: http://dx.doi.org/10.24327/ijrsr.2018.0901.1474

****