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Role of Growth Factors and Their Signaling Cascades in the Etiology of Uterine Fibroids

Ch. Bharathi, Pratibha Nallari and A. Venkateshwari*

Institute of Genetics and Hospital for Genetic Diseases, Osmania University, Begumpet, Hyderabad, Andhra Pradesh, India

*Corresponding Author E-mail: venkateshwari@yahoo.com

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ABSTRACT

Uterine leiomyomas are the benign smooth muscle cell neoplasms of the myometrium, develop in as many as 30% of women aged >35 years during the reproductive years and regress after menopause, indicating ovarian steroid and growth factor dependent growth potential. Most of the uterine cellular functions like cell proliferation, differentiation, angiogenesis and apoptosis are controlled by steroid hormones which mediate their action on target tissues by local production of growth factors acting via paracrine and/or autocrine mechanisms. Thus, indicating that growth factors and their receptors and signaling pathways plays a major role in growth, development and mediate many physiological functions. Derangement in the function of these molecules plays an important role in tumor progression. The present review discusses about the role of growth factors in uterine leiomyoma.

Key words: *Leiomyoma, Tumors, Extra cellular matrix, Angiogenesis, Apoptosis, Receptor Tyrosine Kinase.*

INTRODUCTION

Uterine leiomyomas (fibroids) are the myometrial smooth muscle cell benign neoplasms of the uterus. They are apparent in women of reproductive age which shrink after menopause[1,2]. The overall world-wide prevalence of leiomyomas estimated by National Women's Health Information Center (NWHIC) is 10-20%, according to the study by Cramer *et al*.[3] fibroids prevalence in Indian population is as high as 30%[3]. According to health survey done by Ministry of Health & Family Welfare, Govt. of India, nearly 20-30% of women in reproductive age group has uterine fibroids. At any given time, nearly 15-25 million Indian women have fibroid uterus. Leiomyomas develop due to the overgrowth of smooth muscle and connective tissue which is composed of extracellular matrix (ECM) containing collagen, proteoglycan, fibronectin[1,4]. Leiomyoma development occurs via transformation of normal myocytes to abnormal myocytes and their growth into clinically apparent tumors, morphologically they resemble normal myometrial smooth-muscle cells (MSMCs) at the cellular level, whereas in leiomyomas myometrial mass and cellular morphology are modified.

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They can form single or multiple mutated smooth-muscle tumor nodules of varying size attached and/or within the myometrium which is encircled by extracellular fibrous connective tissue[5,6]. Loss of apoptosis and to undergo normal dedifferentiation leads to leiomyoma formation[7]. They present dysegulated patterns of cellular differentiation due to altered expression of steroid hormones and growth factors[8,9].

SYMPTOMS

The presence of myomas causes morbidity which affects quality of life. Most women with leiomyomas remain asymptomatic and some women develop symptoms depending on the location and size of lesion. The symptoms are abnormal gynaecologic bleeding, heavy or painful menstruation, abdominal bloating, excruciating defecation, back ache, urinary retention, pain during intercourse and infertility. During pregnancy they may result in miscarriage, bleeding, premature labor or interference with the position of the fetus[10,11].

DIAGNOSIS

The diagnosis of the size, number and position of myomas is carried out by trasvaginal sonography. Large myomas are best imaged with a combination of transabdominal and transvaginal sonography, Magnetic resonance imaging is an accurate method to evaluate the size, position, and number of uterine myomas and other imaging techniques include sonography, saline-infusion sonography, hysteroscopy etc.[11].

ETIOLOGY

The definite cause of leiomyoma development is poorly understood. Epidemiological studies reported by Alan *et al.*[12] and William *et al.*[11] suggests that risk is associated with parity, age at menarche, and age at menopause, whereas obesity, late reproductive age, and nulliparity are associated with increased risk for disease progression and other factors possibly responsible for myoma development are genetic factors. The genetic causes include more than 100 genes that are up-regulated and down-regulated in myomas, steroid hormonal factors, growth factors and their receptors, mediate their action through autocrine/paracrine signaling pathways which regulate cell growth, differentiation, proliferation, and mitogenesis in myoma which ultimately results in leiomyoma pathophysiology[11,12].

GROWTH FACTORS AND MYOMETRIUM

Unicellular organisms perform their key functions by interacting directly with the environment, whereas multicellular organisms require the participation of more than one organ to perform their functions. Thus, it is essential to develop a system to communicate and co-ordinate events between cells of the same and different organs. The cells in a multi-cellular organism achieved this by developing a wide array of ligand - receptor interactions which induce specific responses through different signaling mechanisms.

Growth factors and their receptors are made of polypeptides with a wide range of biological effects and are secreted by different types of cells. Growth factors mediate their effects on target cells by interacting with their corresponding cell-surface receptors. They generally act over short distances either in an intracrine, autocrine, juxtacrine, paracrine or endocrine manner with subsequent signaling transmission via signal transduction systems in the cell[13]. As growth factors are essential components which ultimately decide the fate of cells like cellular proliferation, angiogenesis, extracellular matrix formation and apoptosis, over expression of either growth factors or their respective receptors may contribute to tumor initiation.

Hamburger & Cohen *et al*., in 1950s discovered the first two growth factors; Nerve growth factor (NGF) and Epidermal growth factor (EGF) which initiate the identification of a wide array of growth factors involved in different cell signaling cascades and some of them are known to act on myometrial cells. They are: Transforming growth factor (TGF), Fibroblast growth factor (FGF), Vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), Insulin-like growth factor (IGF)[14]. All these growth factors act as ligands of receptor tyrosine kinases

(RTKs) which activates two critical signaling cascades such as the Ras-MAPK/Erk i.e., Ras mediated mitogen-activated protein kinase (MAPK) Extracellular signal-regulated kinases (Erk) and phosphatidylinosite-3 kinase (P13K)-AKT-mTor pathways[15]. TGF-β also acts through activation of the serine/threonine kinase receptors/Smad pathway that affects the growth of virtually all cell types[16]. Fig 1 illustrates the interaction of growth factors, their receptors and subsequent signaling pathways in mediating cellular response. Thus growth factors can act as positive or negative regulators by interacting with their specific membrane receptors which triggers a cascade of intracellular biochemical signals, resulting in the activation and repression of various subset of genes involved in cell growth, differentiation, development and apoptosis in a wide range of biological systems. Genetic aberrations in growth factors, growth factor receptors and their signaling pathways are inextricably linked to developmental abnormalities and to a variety of chronic diseases mostly in tumors. Tumor cells arise as a result of stepwise progression of genetic events that include the unregulated expression of growth factors or components of their signaling pathways.

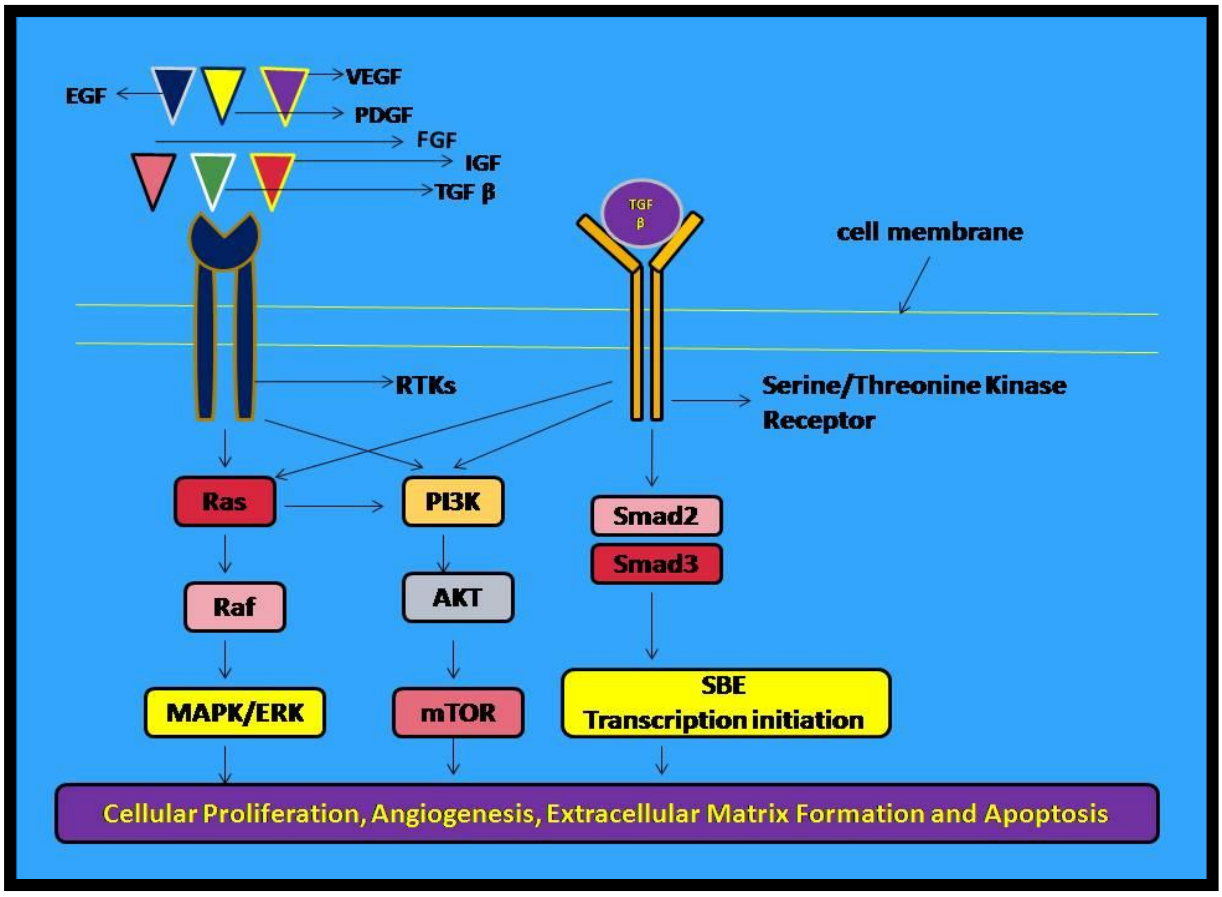

Fig 1: Diagrammatic Representation of growth factors, their receptors and signaling pathways in cellular proliferation, Angiogenesis, Extracellular Matrix Formation and Apoptosis. Different growth factors (EGF, PDGF, IGF, VEGF, FGF, TGF-β) acts as ligands of the RTK and Serine Threonine Kinase Receptors therefore three different signaling cascades such as Ras-Erk/MAPK, PI3K-AKT-mTor and SMAD pathways can be activated. EGF, Epidermal Growth Factor; PDGF, Platelet Derived Growth Factor; IGF, Insulin-like Growth Factor; TGF-β, Transforming Growth Factor-β; VEGF, Vascular Endothelial Growth Factor; FGF, Fibroblast Growth Factor; RTK, Receptor Tyrosine Kinases; MAPK, Mitogen-activated Protein Kinase; PI3K, Phosphatidylinosite-3 Kinase and SMADs.

GROWTH FACTOR RECEPTORS WITH TYROSINE KINASE ACTIVITY

More than 50 receptor tyrosine kinases (RTKs) have been identified till date which is the major type of cell-surface receptors. Upon ligand stimulation of RTK by various growth factors, a number of intracellular signaling pathways are activated, including the cAMP/ PKA Pathway, ERK and JNK signaling, PI-3 Kinase/AKT Pathway, Myc Pathway, NF-kB Pathway and JAK/STAT pathway. The RTKs consists of a large, glycosylated extracellular ligand-binding domain, transmembrane region, and a cytoplasmic portion with protein tyrosine kinase domain. They mediate the transfer of γ-phosphate from adenosine triphosphate (ATP) to tyrosine residues within their own polypeptide chain and to that of exogenous substrates which transduces information carried by the growth factor. The oligomerization of receptor leads to ligand-induced activation of the kinase domain and its signaling thus, stabilizing the interactions between adjacent cytoplasmic domains and controls the activation of kinase activity. Receptor oligomerization appears to be a common phenomenon among growth factor receptors. Dimerization can occur in two ways homodimerization it occurs between two identical receptors and heterodimerization occurs between different members of the same receptor family or a receptor and an accessory protein. The ligand binding to the receptors and induction of oligomerization seems to be specific for each class of RTKs. Thus, ligand binding does not induce receptor dimerization but presumably causes a conformational change in the preformed dimeric receptor, which leads to receptor activation.

The autophosphorylation of specific tyrosine residues in the cytoplasmic portion of the RTK occurs by the activation of intrinsic protein kinase activity thus, leading to a conformational change that facilitates binding of ATP in some receptors and binding of protein substrates in other receptors. The receptor kinase activity then phosphorylates other sites in the cytosolic domain which results in phosphotyrosines serving as docking sites for other proteins involved in RTK-mediated signal transduction[17].

EPIDERMAL GROWTH FACTOR (EGF)

EGF is a 6045-kDa ligand protein that binds to its transmembrane EGF-receptor[18,19] with receptor tyrosine kinase (TK) activity which leads to the activation of inactive receptor monomers to dimerise and autophosphorylate the adjacent intracytoplasmic domains (trans-autophosphorylation), and activation of the intracellular TK activity is accompanied by recruitment of downstream signal transduction molecules that transduces growth signals to MAPK via RAS and BRAF[20], leading to the activation of different pathways that effects the genetic expression, cellular proliferation, inhibition of apoptosis, and angiogenesis. During tumorigenesis, the signaling system is frequently deregulated[21].

Earlier studies showed that EGF is mitogenic for both cultured myometrium and leiomyoma cells and it has been demonstrated that EGF plays an important role in regulating leiomyoma growth[22,23,24]. As it initiates cellular proliferation, angiogenesis and inhibition of apoptosis, this growth factor could play an important role in tumorigenesis in uterine leiomyomas. The fact that the leiomyoma growth occurs by EGF is supported by the AG1478 a selective EGF-R blocker which can block cell proliferation of leiomyoma[25].

Shushan *et al*.[26] demonstrated that leiomyoma cell growth can be blocked by a new EGF-R inhibitor TKS050 which induces cell cycle arrest and apoptosis in a dose- and time-dependent manner. This newly developed inhibitor could act as a possible alternative therapeutic agent for leiomyomas suppression in the years to come[26].

TRANSFORMING GROWTH FACTOR-β (TGF-β)

The molecular weight of TGF- ligand protein is 25-kDa which is a potent regulator of cellular proliferation, differentiation and morphogenesis, as well as extra-cellular matrix formation[27]. TGF-βs mediates its signaling by binding to three different membrane receptors type I, II and III through SMAD dependent and SMAD-independent pathways, such as

Ras/MAPK pathway, JNK pathway and PI3 kinase/Akt pathway that regulates the expression of different types of genes whose products can influence the outcome of leiomyoma growth and regression[28]. It has been hypothesized that TGF-βs, their receptors and downstream signaling mediators, like Smad 2/3 complexes are overexpressed in leiomyoma compared with normal myometrium thus affecting other paracrine and autocrine regulators of cell proliferation and tumor expansion. A study by Pasquapina *et al*.[29] reported that TGF- β3 has shown elevated production of ECM-related genes and low production of ECM degradation-related genes thus inducing a molecular phenotype in myometrial and leiomyoma cells. Arici and Sozen[30] also supported that TGF- β3 induces fibronectin (extracellular matrix glycoprotein) expression in leiomyomas indicating that TGF-β3 may promote the growth of leiomyomas by mediating fibrogenic process which is the characteristic feature of these tumors[29,30]. Thus, TGF- β plays an important role in ECM formation in leiomyomas.

Most of the research has been targeted on TGF-β signaling as a therapeutic approach for treating tumors. Mainly three approaches were found to inhibit the TGF-β signaling pathway they are: (1) Translational Inhibition by antisense oligonucleotides that are engineered into immune cells or directly transferred into tumors (2) Inhibition of ligand-receptor interaction by monoclonal antibodies and (3) TGF-β receptor kinase inhibitors used to inhibit the receptor-mediated signaling cascade. Many drugs have been developed based on these three approaches but are either in non-clinical or in early stages of clinical investigation. Some of them are efficient in restricting the tumor invasion and metastasis in vivo. Few conventional drugs like Rapamycin was found to reinstate the growth-inhibitory activity of TGF-β in cells that have lost this response and can also increase TGF-β induced growth inhibition in responsive cells[31].

FIBROBLAST GROWTH FACTOR (FGF)

There are two types of FGFs; Acidic FGF (aFGF) which is a 16-18 KDa protein and basic FGF (bFGF), an 18 KDa protein[29,32]. FGF initiates mitogenesis, angiogenesis, chemotaxis, differentiation, tissue development and repair, of which bFGF induces mitogenesis and differentiation of fibroblasts and smooth muscle cells of leiomyoma. The FGFs bind to two types of receptors such as fibroblast growth factor type 1 receptor (FGFR-1) and type 2 receptor (FGFR-2)[33]. The FGF system consists of at least 23 growth factors, 4 high-affinity transmembrane receptors with tyrosine kinase activity (FGFRs 1-4) and 1 soluble receptor (FGFR5)[33,34,35] . Alternative splicing generates variants of FGFRs, thus enhancing the interaction of FGFs with their receptors[36]. Subsequent downstream signaling occurs through 2 main pathways via the intracellular receptor substrates FGFR substrate 2 (FRS2) and phospholipase Cg (PLCg), leading ultimately to upregulation of the Ras-dependent MAPK and Ras-independent PI3K–Akt signaling pathways. Other pathways can also be activated by FGFRs, including STAT-dependent signaling[37]. Some researchers reported the expression of bFGF and its receptors FGFR-1 and FGFR-2 in both leiomyoma and myometrial cells with more distinct expression of FGFR-1 in the tumors compared with myometrium[38,39,40,41,42,43,44]. Earlier studies by Hague *et al*.[45] reported an increased or decreased expression of aFGF in leiomyomas[45]. Studies by Wolanska *et al*.[43] observed aFGF mRNA was confirmed in both myometrium and uterine leiomyomas with an increased expression during tumor growth[43]. Study by Wolanska *et al*.[46] reported overexpression of aFGF mRNA during mass myometrium conversion into leiomyoma[46], bFGF is not only mitogenic for both human uterine myometrial and leiomyoma cells[47], it also regulates angiogenesis & can also bind to a component of the extra-cellular matrix of leiomyomas[48,49,50] this could initiate leiomyoma formation by mitogenesis & angiogenesis.

Several therapeutic approaches that disrupt FGF-ligand/receptor activity which includes small-molecule tyrosine kinase inhibitors targeting the ATP-binding site of the intracellular tyrosine kinase domain of FGFRs have been developed. (1) The most commonly used inhibitors are mixed kinase inhibitors, including brivanib, dovitinib, lenvatinib, ponatinib and nintedanib (2) Therapeutic monoclonal antibodies for example, GP369 (Aveo) and HuGAL-FR21 (Galaxy) are being developed in the hope of delivering agents highly specific for a particular FGF ligand or FGFR isoform, thus improving the side-effect profile associated with inhibition of multiple FGFR isoforms. Antibodies can offer the additional advantage of recruiting the immune system to contribute to the antitumor activity via antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity (3) FGF-ligand traps inhibits FGF:FGFR signaling by using a ligand trap to sequester FGF ligand and thus preventing it from binding to FGFRs. FP-1039 is a soluble fusion protein consisting of the extracellular FGFR1-IIIc domain fused to the Fc portion of IgG1 that prevents the binding of FGF1, FGF2, and FGF4 to their associated FGFRs[51].

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

VEGF is a secreted, heparin-binding homodimeric glycoprotein with molecular weight of 46 kDa that consists of six isoforms (VEGF121, VEGF145, VEGF165, VEGF183, VEGF189 and VEGF206)[52,53,54] which stimulates angiogenesis in actively growing tumors and cellular responses by binding to tyrosine kinase receptors, VEGFR-1 and VEGFR-2. VEGF is the most predominantly expressed angiogenic factor in uterine leiomyomas[38,55,56]. The receptors VEGFR-1 and VEGFR-2 have also been identified in the smooth muscle cells of both normal myometrium and leiomyomas[56,57]. Expression of VEGF was found to be more stronger in leiomyomas when compared to adjacent myometrium, suggesting that local angiogenesis might be responsible for the development and growth of fibroids[58]. Hong *et al*.[49] reported that VEGF is significantly more expressed in leiomyosarcoma compared with leiomyoma indicating that angiogenic activity of VEGF enhances the growth of fibroids and disease progression in many carcinomas[39,49,59].

VEGF action can be blocked by three different ways (1) inhibition of endogenous tumor VEGF secretion, its neutralization in the microcirculation, preventing its binding and subsequent signal transduction. Secretion of VEGF can be inhibited by antisense oligonucleotides or expression constructs specific for VEGF which have been successfully used in models of thyroid carcinoma, glioma, and melanoma. (2) Anti-VEGF Monoclonal Antibodies have been developed and demonstrated their efficacy in a wide variety of human tumors in xenograft models and (3) Small Molecule Inhibitors like 3-substituted indolinone compound, SU5416, is a specific and potent catalytic inhibitor of VEGFR protein kinases. It inactivates Flk-1/KDR by binding in the adenine-binding pocket. It is a specific VEGFR inhibitor that has virtually no inhibitory activity against serine threonine protein kinases and tyrosine kinases, such as Src, FGF receptor, Met, and Abl and has little activity against PDGF receptor. At present, SU5416 is the most clinically advanced VEGF RTK-selective tyrosine kinase inhibitor being developed for antiangiogenic treatment of cancer[60].

PLATELET-DERIVED GROWTH FACTOR (PDGF)

PDGF is a 125-amino acid dimeric glycoprotein which forms both homodimers (AA and BB) and heterodimers (AB) linked by disulphide bonds[61,62] secreted by macrophages, endothelial cells, fibroblasts, and vascular smooth muscle cells. It has been implicated in the fibroproliferative response in various diseases. It exists in five different isoforms (PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC and PDGF-DD) that activates cellular responses through two different receptors: PDGFR-α and PDGFR-β with 5 extracellular immunoglobulin loops and an intracellular tyrosine kinase domain[63]. The PDGFR-α, binds to A-, B- and C-chains with high affinity

whereas PDGFR-β, binds to the B- and D-chains[64]. Their structure is similar to structures of oncogenes and cell membrane receptors for other ligands, such as c-fms, c-kit, and flt3 (a VEGF receptor). Their activation leads to induction of several oncogenes, including c-fos and c-myc. PDGF receptor α (PDGFR- α) binds homodimer PDGF-AA and monomers PDGF-A, PDGF-B, and PDGF-C. PDGF receptor β (PDGFR-β) binds homodimer PDGF-BB and monomers PDGF-B and PDGF-D. The PDGF-AB heterodimer binds to both receptors. Ligand binding initiates receptor dimerization and autophosphorylation of tyrosine residues, which stimulates DNA synthesis as well as protein synthesis[64,65,22], increases collagen alpha1 expression and modulates the rate of cell proliferation in myometrium and leiomyoma cells[30,66]. Taniguchi *et al*.[67] examined whether or not PDGF would be able to stimulate the expression of VEGF in cultured human myometrial smooth muscle cells. They reported that PDGF treatment enhanced VEGF immunoreactivity and stimulated cell proliferation[67]. Mesquita *et al*.[68] demonstrated that NADPH oxidase derived ROS is a necessary component of the MAP kinase mitogenic pathway activated by PDGF in leiomyoma smooth muscle cells[68]. Thus PDGF plays a crucial role in cell proliferation, collagen formation in leiomyomas.

The therapeutic approaches are (1) PDGF signaling antagonists under preclinical and clinical evaluation (2) The inhibitors include antibodies, DNA aptamers or soluble extracellular parts of the receptors that bind PDGF isoforms and thus prevent their binding to signaling receptors. Alternatively, antibodies or other binders can target the receptors and prevent their activation or promote their degradation. Another type of antagonists include low molecular inhibitors of the receptor kinases. Several potent inhibitors of PDGF receptor kinases have been developed, including imatinib, sunitinib, sorafenib, pazopanib and nilotinibu can be used in tumor treatment[69].

INSULIN-LIKE GROWTH FACTOR (IGF)

Insulin-like growth factor family consists of six high-affinity IGF binding proteins (IGFBP1–6) with two cell surface receptors (IGF-IR and IGF-IIR) and two ligands (IGFI and IGFII)[70]. They are produced primarily in the liver under the control of the growth hormone. IGF-I is a mitogen for epithelial and mesenchymal cells, and acts as an antiapoptotic agent[71]. It also stimulates collagen synthesis, induces oligodendrocyte development, and supports growth of astrocytoma and meningioma cells in vitro[72] and exhibits autocrine activity in several normal cell types (eg, smooth muscle cells in the media of blood vessels, striated muscle cells and cancer cells)[73,74]. IGFI mediates its action by binding to two receptor tyrosine kinases, IGF-IR and the insulin receptor (at low affinity) as well as their heterodimers, whereas IGFII can bind IGF-IR and it is the sole ligand for the IGF-IIR/mannose 6-phosphate receptor. Currently it is assumed that, although the IGFI axis may not generate strong oncogenic signals, its intactness is essential for survival of transformed cells. It is notable that the receptors of the IGF axis are expressed on most types of tumors, and by recruiting the PI3K-AKT pathway IGF-IR generates extremely potent anti-apoptotic signals[14]. Earlier studies reported IGF-I and IGF-II mRNAs are present in leiomyoma and myometrium as well as in leiomyosarcoma[75,76,77,78], while IGF-I content is higher in leiomyomas than compared to normal myometrium[38,79,80,81]. Strawn *et al*.[82] reported that IGF-I as a mitogenic factor in leiomyoma cell cultures[82]. IGF-I also plays a typical role in the growth of leiomyoma cells, by increasing PCNA expression and up-regulating Bcl-2 in leiomyoma cells[83,84]. Peng *et al*.[85] examined deregulation of IGFs and its signaling pathways as a frequent event in symptomatic leiomyomas and whether they are associated with large fibroids. Their results revealed that IGF-I levels were directly correlated with activation of p-AKT and p-S6K. Larger fibroids showed higher levels of

IGF-I and p-AKT activity when compared with small ones whereas IGF-II has not shown such association[85]. Moreover, IGF promotes increased cellular proliferation in uterine leiomyoma cells by activating the MAPK pathway, and such effect can be reversed by using neutralizing antibody against the IGF-IRb in vitro[80].

IGF-binding proteins inhibit the actions of IGFs by blocking their binding to the receptor. The IGF-IR pathway has been the subject of intensive drug discovery. Recent estimates suggests that as many as 30 agents targeting IGF-IR are in preclinical or clinical development and currently there are at least 58 active clinical trials evaluating anti-IGF-IR targeting agents alone or in various combinations. The two main strategies employed to inhibit the pathway are (1) Antibodies directed against IGF-IR and (2) Small molecule Tyrosine kinase inhibitors (TKIs)[86].

SEX STEROID HORMONE REGULATION OF FIBROIDS

The ovarian steroid hormones, estrogen and progesterone, are considered to be the most significant regulators of leiomyoma growth. Homeostatic control of the net growth of fibroids is the result of dynamic balance between cell proliferation and apoptosis. However, the hidden molecular mechanisms involved in the action of steroid hormones which regulates the proliferation and apoptosis of leiomyoma cells remains to be elucidated. Thus, in this review much attention has been drawn towards the effects of sex steroid hormones on the expression of local growth factors in leiomyoma cells.

ESTROGENS

Estrogen is the most widely involved steroid hormone in the tumorigenesis and growth of leiomyomas. The physiological effects of estrogen on target cells is mediated by binding to its two specific receptors, estrogen receptor α (ER α) and estrogen receptor β (ER β). ER α and ER β shows similar homology in their DNA-binding domain and the ligand-binding domain and can stimulate transcription of the target genes. Estrogen have been shown to upregulate several genes like connexin 43 gap junction protein, type I and III collagen, IGF-I and its receptor, parathyroid hormone-related peptide, and progesterone receptor in leiomyomas when compared to myometrium. Estrogen has shown to mediate its mitogenic effects on leiomyoma cells by triggering the rapid and transient activation of the MAPK pathway and other early downstream signal transduction pathways. Moreover, estrogen mediates its action by growth factors like IGF-I, EGF and PDGF produced by the target cells in the uterus.

Thus therapeutic approach to treat leiomyomas involves GnRH agonist therapy as leiomyomas over-express aromatase p450, an estrogen synthetase, which catalyses androgens to estrogens Shozu *et al*[87]. reported that the expression of aromatase P450 is inhibitted by GnRH agonist therapy in leiomyoma cells, indicating that the suppression of in situ estrogen can be an additional mechanism of GnRH agonist-induced regression of leiomyomas[87].

PROGESTERONES

Progesterone might stimulate the mitogenesis and proliferation of leiomyoma cells by interacting with its two different receptors named, PR-A and PR-B. Both these receptors functions as ligand-activated transcription factors but exhibit distinct biological functions. PR-A acts as a potent ligand-dependent repressor of PR-B transcriptional activity, while PR-B acts as a transcriptional activator of progesterone-responsive genes. Kawaguchi *et al* [88]. observed an increased mitotic activity in leiomyoma at the secretory phase of the cycle, suggesting that the growth of leiomyoma is affected by progesterone levels. A Study by Maruo *et al.*[89] reported that PR-A and PR-B contents are higher in leiomyoma than in adjacent myometrium with a significant dominance of PR-A over PR-B. Therapeutic approaches to treat leiomyoma mainly includes progesterone antagonist RU-486 (mifepristone) which has been reported to induce the regression of leiomyomas[89,90].

CONCLUSION

Sex steroid hormones and growth factors play an important role in normal functioning of uterus by autocrine and paracrine mechanisms. Imbalance in these factors results in improper functioning of uterus thereby resulting in leiomyomas. Therefore it has been hypothesized that overexpression of growth factors by a paracrine mode might increase the proliferation of a polyclonal target cell population. This conceivably could increase the frequency of spontaneous genetic changes in the population, eventually selecting for a tumor cell. Constitutive activation of growth factor signaling pathways by sex steroid hormones through genetic alterations contributes to the development and progression of most if not all human tumors. Thus, future studies on the interactive role of these growth factors and sex steroid hormones need to be elucidated to understand the possible mechanisms involved in the pathogenesis of leiomyomas.

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Conflict of interest

The authors declare that they have no conflict of interest.

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