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Review

A Prominent Action of Insulin-Like Growth Factor I in the Stimulation of Uterine Leiomyomata: A Review

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Abstract

Uterine leiomyomata is a common disease of the female reproductive system. It causes many complications, such as heavy bleeding and menorrhagia. However, the causes of uterine leiomyomata are still unclear. Studies have shown that estrogen, progesterone, and insulin-like growth factor I play key roles in the development of uterine leiomyomata. Abnormal expression of insulin-like growth factor I is believed to be one of the factors that lead to uterine leiomyomata. Uterine leiomyomata are considered benign tumors, which do not lose division control like malignant cells. There are many factors involved in the pathways of uterine leiomyomata onset, such as various growth factors, cytokines, and steroid hormones.

Keywords: Uterine leiomyomata, Insulin-like growth factor I (IGF-I), Estrogen, Progesterone.

Introduction

The uterine leiomyomata (fibroids) are a common type of tumor in the smooth muscle of the uterus (myometrium) in women. The prevalence of uterine leiomyomata is noticeable high in premenopausal women of a certain population [1]. Uterine leiomyomata are considered a significant problem because of hysterectomy in some cases [2]. Many factors increase the incidence chance of uterine leiomyomata, such as the increasing age, many environmental factors such as eating red meat, and smoking; in addition, the probability is more increased in black women than white [3].

Women with uterine leiomyomata are suffering from heavy bleeding during periods, pain in their lower back and pelvis, and have fertility issues [4]. The uterine leiomyomata pathogenesis is not understood, but studies have shown that they arise because of inflammation [5]. 50% of women who have uterine leiomyomata are symptomatic. Women with uterine leiomyomata seek to use alternative treatments to keep their uterus and not get a hysterectomy [6]. Treatments such as uterine artery embolization (UAE) and radiofrequency ablation (RFA) can reduce the volume of fibroids, and therefore, do lead not to hysterectomies [1].

On the other hand, hormone control therapy that can provide medical management for symptomatic uterine leiomyomata in women; this hormone control therapy includes gonadotropin-releasing hormone agonists (GnRH), which can stimulate amenorrhea, and therefore decrease the size of fibroids until they become minimal. However, this medical management has many side effects because of the significant decrease in estrogen level, which causes hot flashes and many other undesirable symptoms. Other hormone control therapies involve estrogen-progesterone hormones, but this treatment does not benefit from the reduction of fibroids growth [7-9]. In postmenopausal women, uterine fibroids are treated with other methods that involve using raloxifene (Evista), which is a selective estrogen receptor modulator. This treatment has demonstrated its ability to reduce the size of fibroids [8, 10]. Uterine leiomyomata are considered to be a disorder that has a nonregulated production of the extracellular matrix (ECM). The progesterone and estrogen hormones perhaps play a role in the establishment and growth of fibroids tumors [11]. Studies have exhibited that women with uterine leiomyomata have

a reduction in the metabolism rate of estrogen, accompanied by increasing estrogen receptors [12-14]. Progesterone and estrogen mechanism of action in uterine fibroids may be accompanied by growth factors [15]; one of these growth factors enclosed with uterine fibroids is the insulin-like growth factor (IGF-I). IGF-I can stimulate the growth of fibroids and stops the mechanism of apoptosis [16]. A study has reported that women with uterine leiomyomata have a high expression of IGF-I compared with healthy women [17]. The endocrine growth factor, which is synthesized in the liver, IGF-I, can regulate both normal and abnormal cell growth. The synthesis of IGF-I is stimulated by growth hormones [18].

Correlation of growth factors with uterine leiomyomata

Growth factors are molecules used as intermediates in various signaling pathways. In fact, they are regulators for many biological activities such as inflammation, cell proliferation, cell growth, and many others. Some of these growth factors are proteins, while others are peptides. They play key roles in uterine leiomyomata formation via different signaling pathways. Many studies have demonstrated their contributions in the pathogenesis of uterine leiomyomata, and molecules like acidic and basic fibroblast growth factors (aFGF and bFGF, respectively), which are growth factors that promote angiogenesis, are found in high concentration in uterine leiomyomata compared with the normal myometrium [19, 20]. Activin A is also a growth factor found in uterine leiomyomata in high concentrations compared with the normal myometrium. Studies have shown that uterine leiomyomata cells have a high expression of the extracellular matrix since the matrix can support the growth of uterine leiomyomata cells. Activin A is one of the growth factors that has elevated expression of the extracellular matrix; besides, Activin A stimulates the Smad transduction pathways [21]. The epidermal growth factor (EGF) stimulates the proliferation of uterine leiomyomata cells because of its mitogenic effect on these cells, which activate the MAPK1 pathway [22]. Heparin-binding EGF (HB-EGF) works against apoptosis of uterine leiomyomata cells [23]. The growth differentiation factor-8 (GDF-8) has exhibited its ability to activate the Smad 2 and 3 signaling pathways, which support the proliferation of leiomyomata cells. The platelet-derived growth factor (PDGF) has shown the ability to induce the expression of collagen. Also, PDGF cooperates with some growth factors to induce the proliferation of leiomyomata cells. The insulin-like growth factors (IGFs) have a prominent role in the enhancement of proliferation, especially the insulin-like growth factor I (IGF-I), which has many activities in the pathogeneses of uterine leiomyomata, such as blocking the apoptosis process and activation of the MAPK and AKT pathways [24].

IGFs and their receptors

IGFs and their receptors are responsible for several functions in different cell types, such as cell differentiation and proliferation; in addition, they have an essential role in apoptosis. IGF-I, IGF-II and insulin with their binding proteins and receptors are considered as a complement system of growth factors [25, 26]. According to a hypothesis [27], the growth hormone (GH) is stimulating the growth action by using another factor; thus, GH stimulates, in fact, the synthesis of IGF-I which binds to IGF-I binding proteins with a high affinity, in order to bind with its receptor [28]. IGF-I is different from other growth factors with its ability to stimulate both the differentiation and proliferation of cells growing in culture [29]. The proliferation action of IGF-I on myoblasts remains for 24-36 h, and then it is followed by myogenic differentiation. There are many events that happen as a result of the IGF-I proliferation induction; the synthesis of DNA increases, the use of amino acids rises, the level of proteins increases, and the number of cells increases as well. In addition, proteolysis is inhibited. IGFs can be recognized by two receptors, the IGF-I and IGF-II receptors. The IGF-I is characterized by its homology to another receptor called the insulin receptor. The degree of homology between the two receptors is considerable. Also, it was observed that the cation independent mannose 6-phosphate receptor is an identical receptor to the IGF-II receptor. Insulin, IGF-I, and IGF-II are bounded to the IGF-I receptor but with different affinity. The IGF-I binds with high affinity, while IGF-II and insulin are bounded with very low affinity. IGF-II and IGF-I are bounded to the IGF-II receptor, but the insulin does not bind. The binding affinity between the IGF-II receptor and IGF-II is very high. The insulin receptor can bind with low affinity with IGFs [30].

IGF-I receptor

Studies have demonstrated that most of the biological activities on cells (such as the growth of cells) that occurred because of IGFs are dependent mainly on the IGF-I receptor's signaling mechanisms.

The IGF-I protein receptor consists of two α subunits and two β subunits. The α-subunit has a binding site that is characterized by a high content of cysteine. The β subunits have intrinsic enzyme activity, which is the tyrosine kinase enzyme. This enzyme becomes active when IGF-I binds to the receptor. IGF-I is mainly responsible for the induction of cell growth and differentiation, whereas insulin is responsible for the metabolism of proteins, carbohydrates, and lipids in mammalian cells. Although both hormones (IGF-I and insulin) have different actions, there is an interfering in their actions [31, 32]. Studies have found a high similarity in the protein levels between the IGF-I receptor and the insulin receptor. The similarity appeared significant in the domain of tyrosine kinase [33]. Although both IGF-I and insulin are binding to their ligands, if the amount of insulin or IGF-I is high, both of them cross-react with the receptor of the other (IGF-I binds with the insulin receptor and vice versa) [34, 35].

The role of IGF-I in the stimulation of uterine leiomyomata

Many studies have reported that there is a close relationship between uterine leiomyomas and IGF-I. The high expression of IGF-I and its receptor (IGF-IR) is leading the cell toward proliferation and prevents apoptosis [36]. A high amount of IGF-1 receptor is leading to increased activation of IGF-I and an increased number of ligands [37]. A study was designed to determine which of either IGF-I or IGF-II leads to the induction of uterine leiomyoma; the researchers added IGF-I and IGF-II on uterine leiomyoma cells. They have found that there is a high elevation in cell proliferation in the uterine leiomyoma cell culture that was provided with IGF-I, while this did not occur with the culture that was treated with IGF-II. On the other hand, IGF-I and IGF-II did not affect the myometrial cells [38].

Steroid hormones stimulate IGF-I; during the reproductive period, progesterone and estrogen levels increase the incidence of uterine fibroids; this is based on clinical conclusions, which have demonstrated that the uterine cell proliferation happened in response to progesterone and estrogen levels. After menopause, progesterone and estrogen are decreased, so the incidence of uterine fibroids decreases [39, 40]. Many in vitro studies have reported several pathways for the interactions between steroid hormones and growth factors, leading to uterine fibroids [17, 41, 42]. Multiple in vivo studies have demonstrated that the expression of IGF-I mRNA was increased significantly by estradiol in the myometrium of rats [43, 44]. The expression of mRNAs of IGF-I and IGF-II was estimated on fibroids and normal human myometrium, and it was higher in fibroids. Moreover, the number of IGF-I binding sites is higher in uterine fibroids, and they exhibited higher affinity compared to normal myometrium [45]. Giudice et al. have reported that the expression of IGF-I mRNAs was very high in women with fibroids in their proliferative periods. This period is distinguished by a high concentration of estradiol, while during the period with a high level of progesterone from a woman's life, the expression of IGF-I mRNAs was decreased, suggesting that the expression of mRNA of IGF-I may be regulated by estradiol in women with uterine fibroids [46]. Also, it has observed that the expression of IGF-I mRNA is very high in the follicular phase. A study that examined a sample of more than one fibroid from one patient showed that the expression of IGF-I mRNA has a notable variation among these fibroids, although they were taken from the same patient. Women who have taken the gonadotropin-releasing hormone (GnRH) as a treatment for uterine fibroids displayed a reduction in fibroids and the level of expression of IGF-I mRNA [47]. Studies investigating fibroids of Eker rats showed that the IGF-I peptide was expressed in a high amount, which is the same as in the case of human patients [47, 48]. Takashi et al. have cultured the leiomyomata cells with the following treatments: progesterone and estradiol, combined with progesterone. The two treatments have decreased the expression of proteins and IGF-I mRNA significantly compared with control leiomyomata cells. On the other hand, another group of cells was treated with estradiol alone, but the results have demonstrated that there is no effect on IGF-I mRNA expression and protein levels [49]. However, in an in vivo study, it was found that IGF-II expression has no relation to steroid hormones [36]. A study conducted to investigate the presence of insulin-like growth factor-binding proteins (IGFBPs) mRNA in both myometrium and leiomyomata cells demonstrated that no IGFBP-1 mRNA was present in leiomyomata and

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myometrium cells, while IGFBP-2 mRNA was found in both types of cells, in identical quantities. The IGFBP-3 mRNA was also detected in both cells, demonstrating a high level in the myometrium compared to leiomyomata cells [50]. In a study on leiomyomata and myometrium cells treated with estrogen, researchers wanted to investigate the signaling pathway of estrogen involved in the development of leiomyomata cells. Moreover, they tried to find new genes that may include in the induction of cell proliferation after exposure to estrogen.

They have concluded that the proliferation of cells in uterine leiomyomata is not only because of the estrogen (as in the case of MCF7 breast cancer) but because of various molecules that stimulate the proliferation of uterine fibroids; they have reported that there are novel genes that cooperate with other genes to induce proliferation. The A-myb gene, which enhances smooth cells' growth, is one of the novel genes that was found to stimulate fibroids formation in the uterus. The level of expression of the A-myb gene is increased significantly after the treatment with estrogen. Thus, the expression of the A-myb gene is dependent on estrogen. Also, it was observed that the A-myb gene is involved in the IGF-I signaling pathway, and it is up-regulated in cells that are exposed to estrogen. The MAPK pathway has an important role in proliferation and apoptosis. IGF-I may induce the elevation of phosphorylated MAPK. The expression of MAPK did not increase due to estrogen exposure. The study has found that in cells exposed to estrogen, the expression of MKP-1 is down-regulated. On the other hand, c-fos and myc genes have exhibited a prominent role in the regulation of the cell cycle. The levels of expression of these genes (c-fos and myc) have demonstrated a down-regulation in the leiomyomata cells treated with estrogen. This study has shown that the genes which are exposed to estrogen-treated leiomyomata are differentially expressed [17]. A study by Peng et al. has reported that there is an abnormality in the signaling pathways for IGF-I and the downstream molecules in some leiomyomata cells. Besides, IGF-I induces the increase of expression of p-AKT [51]. The action of IGF-I includes many effector proteins, which contribute to various signaling pathways. In addition to the above-mentioned mechanisms, P13K is stimulating proliferation and is mediated by various proteins such as receptor tyrosine kinases (RTKs), which play a role in the regulation of the cell cycle. The dysregulation of RTKs is contributing to the formation of uterine fibroids. Studies have shown that the mTOR signaling pathway is continuous in fibroids. On the other hand, IGF-I induces the overexpression of Bcl2 in fibroids [36, 49, 52]. A recent study has revealed that there are epigenetic mutations that contribute to the pathogenesis of uterine leiomyoma; these mutations affect two genes, SATB2 and NRG1. The study has explained that the abnormal methylation of these two genes is believed to play a prominent role in uterine leiomyoma. The two genes are highly expressed in uterine leiomyoma compared to normal myometrium [53]. On the other hand, uterine artery embolization (UAE) is one of the therapies used for uterine leiomyoma. The principle of the UAE is to prevent the uterine leiomyoma from receiving nourishment by blood, which leads to a noticeable decrease in the size of fibroids; thus, this type of therapy stimulates the hypoxia of fibroid cells. The vascular endothelial growth factor (VEGF) is one of the growth factors that is also included in the uterine leiomyoma pathogenesis. VEGF can enhance the division of the vascular endothelial cells, and it was found that the expression of VEGF increased significantly in uterine leiomyoma, leading to the angiogenesis process in uterine leiomyoma. A study tried to predict if there is a possibility for taking into consideration the levels of IGF-I and VEGF as hint factors after treatment using UAE therapy. The IGF-I and VEGF have a high incidence in patients before the UAE therapy. The levels of IGF-I and VEGF were assessed after a short period (one week) in patients that received UAE therapy, and the results have shown that the levels of IGF-I and VEGF were decreased compared with their levels before UAE therapy. However, after a long period (more than one month) of UAE therapy, the levels of IGF-I and VEGF were increased.

This study has concluded that the decreased level of IGF-I and VEGF after UAE therapy prevents disease progression in women who are suffering from uterine leiomyoma for a long period [54]. Many treatments have been used to enhance the shrinkage of fibroids; one of these treatments is mifepristone, which has exhibited clear results in shrinkage of fibroids, but after stopping the treatment, the fibroids develop again. Mifepristone has the ability to control the expression of IGF-I in uterine leiomyoma, but the mechanism is not clear. A study has shown that mifepristone's mechanism in uterine leiomyoma involves not only controlling IGF-I, but also controlling the extracellular signal-regulated kinases (ERK) 1/2, the IGF-I downstream protein [55].

Conclusion

The prevalence of uterine leiomyoma is continuously increasing worldwide. IGF-I is considered an important growth factor involved in the development of this disease. There is an urgent need for more studies to understand profoundly and more clearly the role of IGF-I in the onset of uterine leiomyoma, which may help in the treatment or at least control the disease symptoms as much as possible.

Conflict of Interest

The authors declare that there is no conflict of interest.

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