Vascular Endothelial Growth Factor and Interleukin-1b Possible Correlations with Uterine Leiomyoma

Marwa Kamal Mohamed Abdelghany [1], Haidy Zidan [2], Hala Elsayed Mohamed Mowafy [3], Shereen Mohamed ElShabrawy [2]

1 Medical Biochemistry Department, Faculty of Medicine, Helwan university
2 Medical Biochemistry, Faculty of Medicine, Zagazig university
3 Obstetrics and Gynecology Department, Faculty of Medicine, Zagazig university
Email: Marwaelfeky.me@gmail.com

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Abstract

Background: Vascular endothelial growth factor A (VEGF-A) is a protein that in humans is encoded by the VEGFA gene. This gene is a member of the platelet-derived growth factor (PDGF)/vascular endothelial growth factor (VEGF) family and encodes a protein that is often found as a disulfide linked homodimer. VEGF-A shows prominent activity with vascular endothelial cells, primarily through its interactions with the VEGFR1 and -R2 receptors found in prominently on the endothelial cell membrane. Although, it does have effects on a number of other cell types (e.g., stimulation monocyte/macrophage migration, neurons, cancer cells, kidney epithelial cells). In vitro, VEGF-A has been shown to stimulate endothelial cell mitogenesis and cell migration. VEGF-A is also a vasodilator and increases microvascular permeability and was originally referred to as vascular permeability factor. Interleukin-1b (IL-1b) also known as leukocytic pyrogen, leukocytic endogenous mediator, mononuclear cell factor, lymphocyte activating factor and other names, is a cytokine protein that in humans is encoded by the IL1B gene. There are two genes for interleukin-1 (IL-1): IL-1 alpha and IL-1 beta. IL-1b precursor is cleaved by cytosolic caspase 1 (interleukin 1 b convertase) to form mature IL-1b. Several studies have reported increased expression levels of IL-1b in uterine leiomyoma tissue compared to healthy myometrium. This suggests the involvement of IL-1b in the pathogenesis and growth of leiomyomas. Uterine leiomyoma is associated with a chronic inflammatory microenvironment, characterized by infiltrating immune cells. IL-1b has been shown to promote this inflammatory environment through its ability to induce the expression of pro-inflammatory factors.

Keywords: Vascular Endothelial Growth Factor, Interleukin-1b, Uterine Leiomyoma

Introduction

Uterine leiomyomas (ULMs) (also referred to as fibroids or myomas) are the most common pelvic tumour in women .They are benign tumours arising from the smooth muscle cells of the myometrium. They arise in reproductive-age women and typically present with symptoms of abnormal uterine bleeding and/or pelvic pain/pressure. Uterine leiomyoma may also have reproductive effects (eg, infertility, adverse pregnancy outcomes **(1)**.

The economic impact of leiomyomas is profound, affecting an estimated 11 million women **(2)**

There are notable racial differences in the prevalence and presentation of leiomyomas. For example, leiomyomas are more common and are greater in number, and larger in size in women of African ancestry versus white or Asian women. **(3)**.

The risk factors, that are associated with the development of ULMS include both modifiable and non-modifiable factors. These factors include age, race., genetic pattern ., environmental factors and lifestyle (diet, caffeine and alcohol consumption, physical activity, stress, and smoking), steroid hormones (endogenous and exogenous) and growth factors. All these factors play a role in the formation and growth of uterine leiomyomas. **(4)**.

Uterine leiomyomas are noncancerous monoclonal neoplasms arising from uterine smooth muscle cells and fibroblasts They contain a large amount of extracellular matrix (including collagen, proteoglycan, fibronectin) and are surrounded by a thin pseudocapsule of areolar tissue and compressed muscle fibers**.(5)**

In the National Institute of Environmental Health Sciences **(** NIEHS) Uterine leiomyoma Study was initiated to gain insight into the pathogenesis of these tumors and to correlate their molecular characteristics with their histology. the observations led to that the early development of fibroids might be predominantly proliferative, and that the collagenous matrix was variable from one tumor to another but sometimes was remarkably abundant with reduction in the myocyte cellularity. On this basis, fibroid growth divided into four phases, with phase 1 tumors having the least collagen and phase 4 tumors the most . **(6)**

Vascular endothelial growth factor was originally described as an endothelial cell-specific mitogen. VEGF is produced by many cell types including tumor cells, macrophages, platelets, keratinocytes, and renal mesangial cells. The activities of VEGF are not limited to the vascular system; VEGF plays a role in normal physiological functions such as bone formation, hematopoiesis, wound healing, and development**.** Angiogenesis is main features of benign and malignant tumours. VEGF is one of the most powerful endothelial cell mitogen and has a very critical role in normal physiological and tumor angiogenesis . It enhances tumour vessel permeability and endothelial cell proliferation, migration, differentiation, capillary formation and also has proinflammatory actions **(7).**

VEGF has immunoreactivity effect on tumour cells and stromal matrix. This may contribute to tumour cell growth in a paracrine manner through angiogenesis and increased vascular permeability. Continuous exposure to VEGF may potentially increase the effect of other risk factors such as sex hormones that increase vascular supply of the ovary and enhance development of leiomyomas. **(8)**.

The contribution of VEGF to tumor angiogenesis is well understood. VEGF is up-regulated in many tumors and VEGF protein was detected in the culture media from a range of tumor cell lines . VEGF mRNA was also detected in numerous tumors and metastases, with immunoreactivity for VEGF localized on tumor cells and in the stromal matrix. VEGF might be released into the surrounding stromal matrix, which might contribute to tumor growth and metastasis in a paracrine manner through angiogenesis and increased vascular permeability. Some investigators have reported no correlation between serum VEGF levels and tumor vascular density. These findings suggested VEGF may promote tumor growth by direct pro-survival effects in tumor cells .Given the involvement of VEGF in uterine leiomyoma pathogenesis, targeting this factor has emerged as a potential therapeutic strategy. Preclinical studies using anti VEGF or VEGF receptor antagonists have shown promise in attenuating leiomyotic growth**. (9)**

Types

VEGF-A

Vascular endothelial growth factor A (VEGF-A) is a protein that in humans is encoded by the VEGFA gene. This gene is a member of the platelet-derived growth factor (PDGF)/vascular endothelial growth factor (VEGF) family and encodes a protein that is often found as a disulfide linked homodimer. VEGF-A shows prominent activity with vascular endothelial cells, primarily through its interactions with the VEGFR1 and -R2 receptors found in prominently on the endothelial cell membrane. Although, it does have effects on a number of other cell types (e.g., stimulation monocyte/macrophage migration, neurons, cancer cells, kidney epithelial cells). In vitro, VEGF-A has been shown to stimulate endothelial cell mitogenesis and cell migration. VEGF-A is also a vasodilator and increases microvascular permeability and was originally referred to as vascular permeability factor. VEGF-A is a glycosylated mitogen that specifically acts on endothelial cells and has various effects, including mediating increased vascular permeability, inducing angiogenesis, vasculogenesis and endothelial cell growth, promoting cell migration, and inhibiting apoptosis. Alternatively spliced transcript variants, encoding either freely secreted or cell-associated isoforms, have been characterized. **(10)**.

VEGF-B

Vascular endothelial growth factor B also known as VEGF-B is a protein that, in humans, is encoded by the VEGF-B gene. VEGF-B is a growth factor that belongs to the vascular endothelial growth factor family. In contrast to VEGF-A, VEGF-B plays a less pronounced role in the vascular system: Whereas VEGF-A is important for the formation of blood vessels; VEGF-B seems to play a role only in the maintenance of newly formed blood vessels during pathological conditions **(11)**.

VEGF-C

Vascular endothelial growth factor C (VEGF-C) is a protein that is a member of the platelet-derived growth factor / vascular endothelial growth factor (PDGF/VEGF) family. The main function of VEGF-C is in lymphangiogenesis. However, in addition to its effect on lymphatic vessels, it can also promote the growth of blood vessels and regulate their permeability **(12)**.

VEGF-D (FIGF)

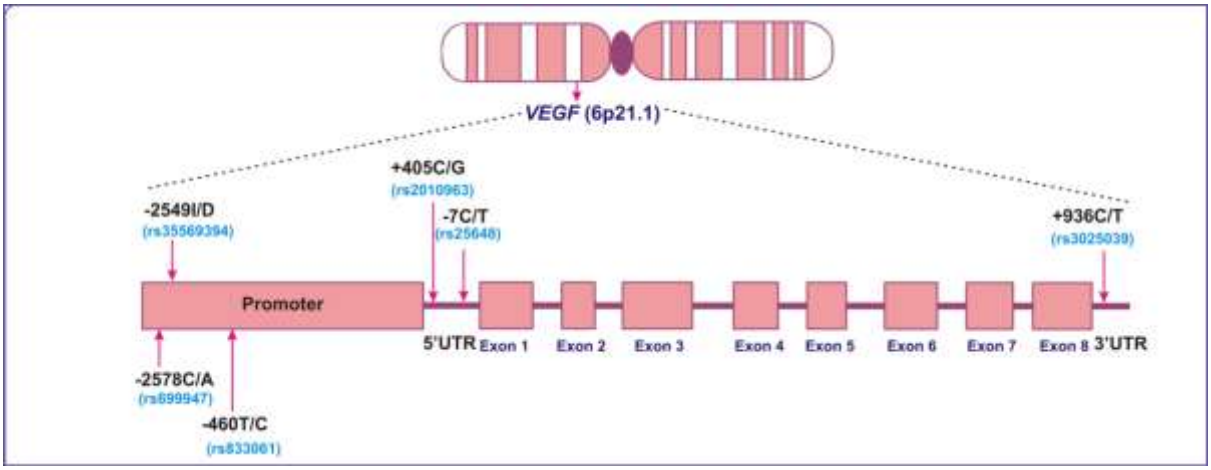
C-fos-induced growth factor (FIGF) (or vascular endothelial growth factor D, VEGF-D) is a vascular endothelial growth factor that in humans is encoded by the FIGF gene. The protein encoded by this gene is a member of the platelet-derived growth factor/vascular endothelial growth factor (PDGF/VEGF) family and is active in angiogenesis, lymphangiogenesis, and endothelial cell growth. VEGF-D's interactions with VEGFR-3 predominantly expressed in lymphatic vessels play a key role in restructuring lymphatic channel .**(13)**.

PGF

Placental growth factor is a protein that in humans is encoded by the PGF gene. PGF is a member of the VEGF (vascular endothelial growth factor) sub-family - a key molecule in angiogenesis and vasculogenesis, in particular during embryogenesis. PGF plays a role in trophoblast growth and differentiation. **(14)**

Chromosomal structure of VEGF-A

VEGF is located at 6p21.3 and it comprises eight exons and seven introns. **(15)**



Figure(1):

It is highly polymorphic with several polymorphisms in the promoter, 5′-untranslated region (5′- UTR) and 3′-UTR . Polymorphisms in the promoter and UTRs have been reported to regulate VEGF expression via alternative initiation of transcription and internal initiation of translation . Functional genetic polymorphisms which alter the regulation of gene expression are predicted to have a signifcant impact on disease pathogenesis −460T/C polymorphisms has proved to increase expression of VEGF**.(16).**

Relation between VEGF and other diseases :

VEGF and its receptors, VEGFR-1 and VEGFR-2, are overexpressed in many human hematopoietic tumor cell lines, and in bone marrow failure states such as chronic myleomonocytic leukemia. **(7).**

Ovarian carcinoma cells were the first non-endothelial tumor cells shown to express VEGFR-2. Pancreatic cancer is extremely aggressive with very poor prognosis. VEGF expression was demonstrated in pancreatic cancer, and both VEGF and VEGF receptor expression was elevated in pancreatic tumor cells in comparison to normal pancreatic tissue**(17)**.

In another malignancy, mesothelioma, which responds poorly to treatment, a VEGF autocrine loop appears to directly stimulate tumor cell growth. As with ovarian cancer and pancreatic cancer, malignant pleural mesothelioma (MM) cells produce VEGF and express VEGFR-1 and VEGFR-2 **(18)**.

VEGF-A and the corresponding receptors are rapidly up-regulated after traumatic injury of the central nervous system (CNS).This would suggest that VEGF-A / VEGF165 could be used as target to promote angiogenesis after traumatic CNS injuries.VEGF is also a biomarker for the diagnosis of acute ischemic stroke **(19)**.

Cytokines

Cytokines are small secreted proteins released by cells have a specific effect on the interactions and communications between cells. Cytokine is a general name; other names include lymphokine (cytokines made by lymphocytes), monokine (cytokines made by monocytes), chemokine (cytokines with chemotactic activities), and interleukin

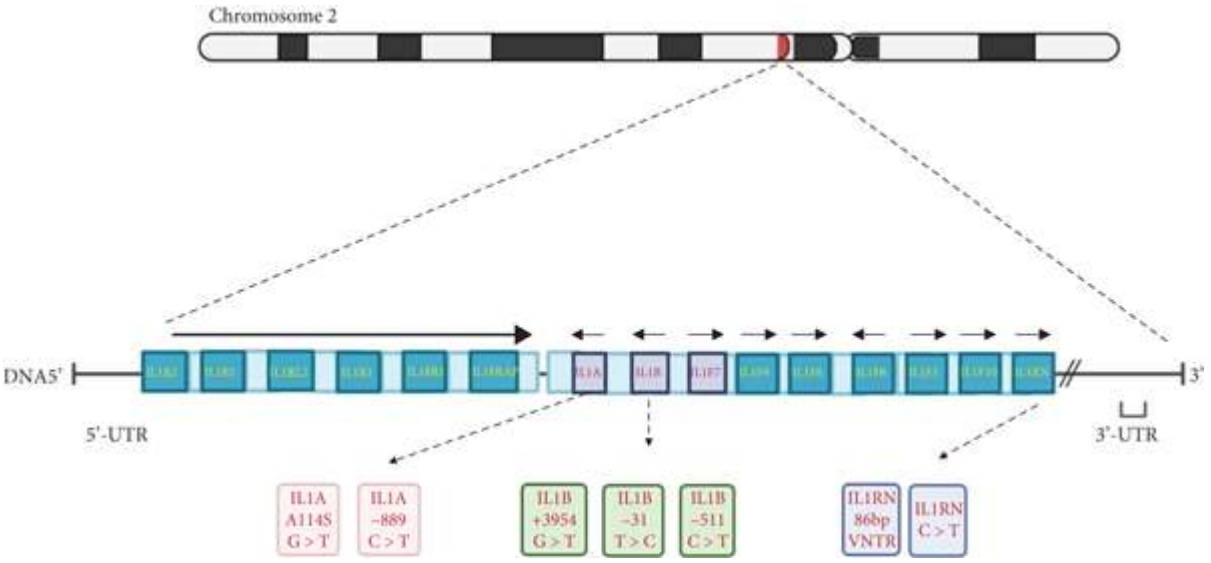
(cytokines made by one leukocyte and acting on other leukocytes). Cytokines may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action) **(20)**.
Cytokines are made by many cell populations, but the predominant producers are helper T cells (Th) and macrophages. Cytokines may be produced in and by peripheral nerve tissue during physiological and pathological processes by resident and recruited macrophages, mast cells, endothelial cells, and Schwann cells. Following a peripheral nerve injury, macrophages and Schwann cells that gather around the injured site of the nerve secrete cytokines and specific growth factors required for nerve regeneration. Localized inflammatory irritation of the dorsal root ganglion (DRG) not only increases pro-inflammatory cytokines but also decreases anti-inflammatory cytokines **(21)**.

Proinflammatory cytokines are produced predominantly by activated macrophages and are involved in the up-regulation of inflammatory reactions. There is abundant evidence that certain pro-inflammatory cytokines such as IL-1b, IL-6, and TNF-α are involved in the process of pathological inflammations. **(22)**.

IL-1b is released primarily by monocytes and macrophages as well as by nonimmune cells, such as fibroblasts and endothelial cells, during cell injury, infection, invasion, and inflammation. cytokines such as Interleukin-1b (IL-1b) have been studied extensively due to their involvement in inflammation and tissue remodeling. **(23).**

Interleukin-1b
Interleukin-1b (IL-1b) also known as leukocytic pyrogen, leukocytic endogenous mediator, mononuclear cell factor, lymphocyte activating factor and other names, is a cytokine protein that in humans is encoded by the IL1B gene. There are two genes for interleukin-1 (IL-1): IL-1 alpha and IL-1 beta. IL-1b precursor is cleaved by cytosolic caspase 1 (interleukin 1 b convertase) to form mature IL-1b **(24)**
IL-1b has important homeostatic functions in the normal organism, such as in the regulation of feeding, sleep, and temperature However, overproduction of IL-1b is implicated in the pathophysiological changes that occur during different disease states, such as rheumatoid arthritis, neuropathic pain, inflammatory bowel disease, osteoarthritis, vascular disease, multiple sclerosis, and Alzheimer's disease .IL-1b can be released from keratinocytes, fibroblasts, synoviocytes, endothelial, neuronal, immune cells such as macrophages and mast cells, and glial cells such as Schwann cells, microglia and astrocytes **(25)**.
Several studies have reported increased expression levels of IL-1b in uterine leiomyoma tissue compared to healthy myometrium. This suggests the involvement of IL-1b in the pathogenesis and growth of leiomyomas**. (25).**
Uterine leiomyoma is associated with a chronic inflammatory microenvironment, characterized by infiltrating immune cells. IL-1b has been shown to promote this inflammatory environment through its ability to induce the expression of pro-inflammatory factors.Genetic variations in the IL-1b gene have been investigated in relation to susceptibility to uterine leiomyoma. Some studies have reported an association between certain IL-1b polymorphisms and an increased risk of developing leiomyomas**. (26).**
Experimental studies have demonstrated that IL-1b can stimulate the proliferation of fibroid cells in vitro. This cytokine promotes cell cycle progression and inhibits apoptosis, thereby contributing to the growth of uterine leiomyoma**.** IL-1b has been implicated in the dysregulation of extracellular matrix (ECM) remodeling processes in uterine leiomyoma. It can stimulate the production of matrix metalloproteinases (MMPs) and modulate the synthesis of ECM components, leading to altered tissue architecture. **(27).**
IL-1b has been shown to promote angiogenesis, the formation of new blood vessels, in uterine leiomyoma. This cytokine can enhance the expression of angiogenic factors, facilitating the vascularization of leiomyotic tissue**.** IL-1b may contribute to leiomyoma-associated symptoms such as pain, abnormal uterine bleeding, and menstrual irregularities. Its pro-inflammatory effects on the uterus and surrounding tissues, coupled with its impact on vascularization, may play a role in symptomatology**. (28).**
Given the involvement of IL-1b in uterine leiomyoma pathogenesis, targeting this cytokine has emerged as a potential therapeutic strategy. Preclinical studies using IL-1b inhibitors or IL-1 receptor antagonists have shown promise in attenuating leiomyotic growth**. (24)**
Pregnancy with uterine leiomyoma can be complicated, and IL-1b may contribute to adverse pregnancy outcomes such as miscarriage, preterm birth, and fetal growth abnormalities. Further research is needed to understand the mechanisms and clinical implications**. (29).**
Chromosomal structure of IL1b :

IL-1 gene family consists of a cluster of classical cytokine agonists that is located on chromosome 2 in two distinct clusters and is reported to contain about 1,500 SNPs .
IL-1b gene is about 7.5 kb long, contains seven exons, and it is regulated by 5' and 3'–UTR regions . it is the second gene displaying several polymorphisms in its sequence, with almost 144 SNPs reported **(30).**



Role of Interleukin-1b in inflammation:
Breifly,IL-1 is a master regulator of inflammation via controlling a variety of innate immune processes . IL-1 has a wide range of biological functions, which include acting as a leukocytic pyrogen, a mediator of fever and a leukocytic endogenous mediator, and an inducer of several components of the acute-phase response and lymphocyte-activating factor (LAF).**(31)**

Activation of IL1b (Inflammasome):
The inflammasome is an intracellular multi-protein complex that is emerging as an important regulator of inflammation (Fig.2). The inflammasome acts as an activating scaffold for proinflammatory Caspases. One such Caspase, Caspase 1, cleaves and activates pro-IL-1b and pro-IL-18 . IL-33 has also been shown to be a possible Caspase 1 substrate . Inflammasomes play important roles in the innate immunity pathway and are active players in inflammatory disorders. As shown below, there is also evidence that they are involved in painful conditions **(32)**.

Inflammasomes contain NOD-like receptor (NLR) proteins, and are named based on which NLR protein is present. The NLRP3, also known as NALP3 or CIAS1, inflammasome is probably the best studied .The NLRP3 protein contains four distinct domains, a Pyrin domain (PYD) at the N-terminus, followed by a NACHT domain (named after NAIP, CIITA, HET-E, and TP1), a NACHT-associated domain (NAD) and a Leucine-rich repeats (LRR) domain at the C-terminus **(33)** .
It is thought that NLRP3 acts as a sensor for cell injury and microbial components and once activated it binds through the PYD region to the ASC (apoptosis-associated speck-like protein containing a CARD domain) adaptor protein, which contains a PYD domain at the N-terminus and a CARD domain at the C-terminus. Besides binding to ASC, NLRP3 is also bound through its NACHT domain to the FIIND domain at the N-terminus of the Cardinal protein **(34)**.
The ASC and Cardinal proteins, through their CARD domains, in turn bind to the CARD domain of pro-Caspase 1, causing proteolytic cleavage yielding activated Caspase 1. Cleaved Caspase 1 can then process pro-IL-1b to its bioactive IL-1b form. Besides Caspase 1, there is evidence that metalloproteases (MMPs) cleave IL-1b, therefore Caspase 1-independent pathways may also play roles in pain transmission **(35)**.

IL-1b in inflammatory diseases
. An expanding spectrum of acute and chronic non-infectious inflammatory diseases is uniquely responsive to IL-1b neutralization. IL-1b-mediated diseases are often called "auto-inflammatory" and the dominant finding is the release of the active form of IL-1b driven by endogenous molecules acting on the monocyte/macrophage**.** Bursts of IL-1b precipitate acute attacks of systemic or local inflammation, IL-1b also contributes to several chronic diseases. For

example, ischemic injury, such as myocardial infarction or stroke, causes acute and extensive damage, and slowly progressive inflammatory processes take place in atherosclerosis, type 2 diabetes, osteoarthritis and myeloma**. (36).** Establishing the role for IL-1b in inflammatory diseases has succeeded by using short-term IL-1b-blockade and its role and usefulness will likely increase with clinical testing**.** Continued research on the relationship between VEGF, IL-1b and uterine leiomyoma is essential for uncovering the underlying mechanisms and identifying potential therapeutic targets. Additionally, investigating the interplay between VEGF,IL-1b and other molecular pathways involved in leiomyoma development could provide further insights into disease progression**.(37).**

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