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Inflammation as a Factor Initiating the Growth of Uterine Fibroids

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Abstract This review shows the leading role of inflammation, its mediated activation of immune cells (macrophages, T1 helper cells, and others) and overexpression of proinflammatory cytokines in the growth of uterine fibroids. Cytokines stimulate angiogenesis and cell proliferation, lead to fibrous changes and remodeling of the extracellular matrix in fibroid tissue. Inflammation control may serve as a special target in the treatment strategy for uterine fibroids, which requires a more detailed consideration of the place of inflammation in the pathophysiology of fibroids in subsequent studies.

Keywords Uterine fibroids, Inflammation, Macrophages, Cytokines, Myofibroblasts

1. Introduction

Uterine fibroids (leiomyomas) are benign tumors that originate from the myometrium and include smooth muscle and connective tissue. The prevalence of uterine fibroids ranges from 25% in women of reproductive age to 70% in premenopausal women, with serious complications requiring surgery, mainly hysterectomy, occurring in about 25% of cases [1]. The growth of fibroids disrupts the configuration of the uterus, the structure of its tissue and leads to a symptomatic manifestation of the disease with heavy menstrual bleeding and subsequent iron deficiency anemia, pelvic pain, impaired function of neighboring organs (flatulence, urination disorders) [2]. Uterine fibroids have a negative impact on reproductive outcomes, including the risk of recurrent miscarriage, premature birth, surgical delivery, postpartum hemorrhagic and purulent-septic complications [3,4], as well as impaired fertility [5]. Uterine fibroids are a significant problem for health and, consequently, quality of life due to an increased risk of hysterectomies, which are performed in a third of cases due to uterine fibroids [6].

It has been proven that sex steroids are crucial for the development and maintenance of fibroid growth. Estradiol and progesterone initiate the formation of mitogenic effects by mature myocytes, to which neighboring immature, undifferentiated myometrial cells respond with the growth of a fibroid node. Contrary to the beliefs that existed until recently, new data indicate the combined effect of estradiol and progesterone in maintaining the growth of the myomatous node. The action of progesterone is aimed at the proliferation of fibroid cells, and estradiol increases the availability of progesterone receptors inside cells [7]. Inflammation may be a necessary link in the pathogenesis of uterine fibroids. There is evidence indicating an increase in the expression of pro-inflammatory cytokines in uterine fibroids [8]. These cytokines can interact with a number of growth factors and affect the growth of fibroids, which is regulated by estrogen and progesterone. Despite the available data, the pathophysiology of uterine fibroids remains unclear and requires further study.

The aim of the study was to determine the place of the inflammatory factor in the pathogenesis of uterine fibroids.

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2. Materials and Methods

The analysis of literary sources of recent years has been carried out using the PubMed, Medline, WHO and Medscape databases.

3. The Results of the Study

Uterine leiomyoma is a monoclonal tumor that occurs under the influence of gene mutations in smooth muscle tissue from a single progenitor cell, or fibroid stem cells [9]. It is believed that in myometrial stem cells, the Wnt protein, whose secretion depends on estrogen, stimulates β-catenin. The activated Wnt/β-catenin signaling pathway is responsible for cell proliferation and preservation of tissue homeostasis [10]. In somatic mutation with enhanced function of the mediator complex subunit 12 (MED12) gene, β-catenin regulation is disrupted [11], which can lead to uncontrolled proliferation of leiomyoma cells [12]. The cellular composition of the resulting tumor clone is heterogeneous and includes smooth muscle cells, vascular smooth muscle cells, fibroblasts, and myofibroblasts [13]. It is suggested that uterine hypoxia, abnormal methylation, or abnormal estrogen signaling may play a crucial role in the transformation of myometrial stem

cells into fibroid stem cells [14]. Further proliferation and clonal expansion occurs in response to steroid hormones via paracrine signaling originating from the surrounding differentiated cells of the myometrium and leiomyoma.

Chronic inflammation occupies a special place in the pathophysiology of uterine fibroids. It has been suggested that an inadequate inflammatory response promotes the transition of myometrial smooth muscle cells into a myofibroblast, a more proliferating phenotype, i.e., the addition of an additional fibrotic function gives this cell proliferating qualities. Cellular transformation into the myofibroblastic phenotype is the key to the establishment and progression of fibrogenesis [15].

Myofibroblasts are activated by inflammation, injury or mechanical action on tissues, hypoxia and oxidative stress. In normal transient inflammation, fibroblasts transform into myofibroblasts and produce extracellular matrix proteins such as collagen, fibronectin, and versican, which are aimed at repairing and restoring tissue homeostasis [16]. However, chronic inflammation in the uterus leads to inappropriate activation of fibroblasts, disrupts the processes of apoptosis of these cells, excessive accumulation of extracellular matrix and fibrosis occurs, which is emphasized in a number of studies as one of the important aspects of the pathogenesis of uterine fibroids [17]. It has been shown that uterine fibroids include 50% more extracellular matrix than peripheral myometrium, which confirms that uterine leiomyoma is a typical fibrous pathology [18]. It is assumed that the extracellular matrix serves as a reservoir for growth factors, cytokines, chemokines, angiogenic mediators and proteases, which are considered as growth stimulators of uterine fibroids [19].

More and more evidence indicates that local chronic inflammation creates a microenvironment that promotes the development of uterine fibroids. Consideration of the chronic inflammatory condition as a central link in the pathophysiology of uterine fibroids is confirmed by the presence of high expression of proinflammatory cytokines in fibroids, including interleukin (IL)-1β, IL-6, IL-13, IL-15, tumor necrosis factor (TNF)-α, granulocyte-macrophage colony-stimulating factor (GM-CSF) and erythropoietin, which interact with estrogens and progesterone, initiating the growth of fibroids [20]. Moreover, the presence of macrophages, lymphocytes, leukocytes and other immune cells in uterine fibroids was revealed, which is relatively more than in the peripheral tissue from the node [20].

Single-cell RNA sequencing has identified various populations of immune cells, such as T cells, natural killer (NK) cells, and B cells in uterine fibroids. Increased regulation of genes involved in leukocyte migration, cytokine production, and regulation of the inflammatory response in uterine fibroids compared with normal myometrium has been identified [13]. A significantly high number of naive CD4+ and central memory T cells, regulatory T cells, cytotoxic T cells, and T1 helper cells were detected in fibroids, while the number of terminal effector memory cells, NK cells, and T2 helper cells was significantly reduced compared to women without uterine fibroids [21]. Also, using the method of mass cytometry, a significantly greater presence of NK cells, common macrophages, M2 macrophages, and ordinary dendritic cells was found inside the fibroid node and surrounding tissue compared with the peripheral myometrium [8].

Despite the presence of resident tissue macrophages, in response to inflammation or damage, monocytes and macrophage precursors are released from the bone marrow and enter the damaged area [22]. Signals transmitted by cytokines and growth factors lead to the proliferation of both newly arrived and resident macrophages. Macrophages are polarized into M1 or M2 macrophages [23]. M1 macrophages are a “pro-inflammatory phenotype" that produce chemokines, matrix metalloproteinases (MMPs), and other inflammatory mediators in response to inflammation. In addition to cytokines, M1 macrophages secrete several growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-β1 (TGF-β1), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor-alpha (VEGF-α) [24].

These molecules stimulate cell proliferation and angiogenesis, the transformation of fibroblasts into myofibroblasts, which is necessary for the healing of the damaged area, in particular, through the production of extracellular matrix components [19]. Next, macrophages are polarized into M2 macrophages, which are considered an “anti-inflammatory phenotype” and produce anti-inflammatory cytokines to suppress and resolve inflammation. Prolonged activation of M1 macrophages leads to continuous production of pro-inflammatory mediators, which contributes to persistent inflammation and progression of tissue fibrosis [25].

Zannotti A, et al. [26] proposed a possible phase mechanism of leiomyoma development, according to which cellular leiomyoma, considered as the first step in tumor transformation, contains low levels of extracellular matrix proteins, but a higher level of infiltration of CD68-positive macrophages, as well as leukocytes and mast cells [20], which may be a response to an inflammatory stimulus. During inflammation, some cells of the cellular leiomyoma transform into myofibroblasts, followed by increased production of extracellular matrix proteins [17]. This is confirmed by the fact that a common leiomyoma, which can be considered a late-phase tumor, contains more extracellular matrix mass and a reduced number of macrophages [20].

Differentiation of myofibroblasts can be caused by several cellular pathways, signals from neighboring cells, including cytokines, steroid hormones and growth factors, and physical factors such as extracellular matrix stress [25]. Cytokines are signaling peptides produced by many immunocompetent cells. They bind to specific receptors on target cells to transmit signals that activate numerous genes involving transcription factors from the family of nuclear factors, such as nuclear factor kappa B (NF-κB) [27]. This process regulates cell proliferation, growth, and apoptosis. Cytokines also interact with growth factors and determine the remodeling processes of the extracellular matrix [20].

Comparison of myometrial progenitor cells and myometrial fibroid progenitor cells showed that myometrial progenitor

cells exhibit significantly higher levels of Th2 pathway cytokines and significantly lower levels of Th1/Th17 cytokines [14]. Increased levels of G-CSF, IL-1α, IL-1β, IL-6 and VEGF-A were found in women with uterine fibroids, compared with those in healthy individuals [28]. Similarly, another study found pronounced trends in the expression of interferon α2, IL-1α, and platelet growth factor AA (PDGF-AA), but significantly lower levels of GM-CSF and IL-1 receptor antagonist (IL-1RA) in patients with uterine fibroids [8].

TNF-α is a key pro-inflammatory cytokine that plays an important role in infection control and antitumor effects. TNF-α expression levels were higher in uterine fibroids compared with peripheral myometrium, moreover, serum TNF-α levels were significantly higher in women with symptomatic uterine fibroids than in healthy individuals, and TNF-α levels correlated with tumor size [29]. There is also evidence indicating that there are no differences in TNF-α levels in women with uterine fibroids compared with healthy individuals [30]. TNF-α increases the expression of matrix metalloproteinase (MMP)-2, stimulates cell migration by activating the kinase signaling pathway, and activates the NF-κB signaling pathway in fibroid smooth muscle cells [31]. These data indicate that TNF-α expression caused by inflammation plays an important role in cell migration and extracellular matrix remodeling in fibroids.

IL-1β is a potent pro-inflammatory cytokine and plays a crucial role in several inflammatory and autoimmune diseases. In uterine fibroids, IL-1β is involved in extracellular matrix remodeling, activates mesenchymal stem cells and the NF-κB pathway [32]. In a review by Ishikawa H, et al. [9] indicated a significant decrease in the expression of IL-1β, IL-6, and IL-10; and a significant increase in the expression of cyclooxygenase (COX)1, COX2, and VEGF in the endometrium of women with uterine fibroids, which is associated with increased regulation of inflammatory pathways in the endometrium. In contrast, Plewka A, et al. [33] noted an increase in the levels of IL-1β and NF-κB in uterine fibroids compared with healthy myometrium in women of reproductive and perimenopausal age. Higher levels of IL-1b were associated with large fibroids in women of reproductive age, whereas no such association was found in perimenopausal age. In addition, there was no correlation between the level of NF-kB and the size of fibroids [33]. An immunohistochemical analysis conducted by de Mezer M, et al. [34] determined that the level of IL-1β was significantly lower in the fibroid thickness compared with the surrounding myometrium and myometrial tissue samples in healthy individuals. The authors noted a significant positive correlation between the concentration of IL-1β and a decrease in the level of NF-kB in the fibroid center [34].

Interleukin 6 (IL-6) is a pleiotropic cytokine, has pro-inflammatory properties, and at the same time regulates inflammation, demonstrating an anti-inflammatory effect. A decrease in the level of IL-6 in the endometrial tissue of women with uterine fibroids has been reported [9]. There are also data showing the absence of significant differences in the level of IL-6 in the blood serum of women with and without uterine fibroids [35]. In another study, IL-6 levels measured in uterine fibroids, peripheral myometrium, and healthy uterine tissue did not differ significantly [34]. Thus, it is possible that IL-6 does not play a role in the development of uterine fibroids, but these data should be clarified in further studies.

The central participant in myofibroblastic differentiation is transforming growth factor-β (TGF-β). TGF-β1 triggers the production of alpha smooth muscle actin (α-SMA) in fibroblasts, which leads to their differentiation into myofibroblasts [36]. α-SMA is a protein that participates in the contraction of smooth muscles and the creation of mechanical stress in cells [37]. Increased expression of TGF-β in the blood serum of women with fibroids was revealed, and the size of fibroids was tightly correlated with the level of TGF-β [38]. Для миомы матки характерно повышение уровня TGF-β3 [39]. Significantly higher levels of TGF-β3 in fibroids and blood serum were found in women with symptomatic fibroids than in healthy individuals, and these levels decreased significantly after administration of ulipristal acetate (UPA), a selective progesterone receptor modulator [36]. Experimental studies have shown that UPA reduces the size of fibroids by inhibiting TGF-β3-mediated extracellular matrix formation in cultured fibroid cells [39]. In addition, there was a significant decrease in the number of cells expressing IL-6 and IL-10 in uterine fibroids with a reduction reaction to UPA, compared with in fibroids without a reaction [40]. All this indicates that the inhibition of TGF-β3 expression under the influence of UPA causes its anti-inflammatory effect and is one of the possible mechanisms for reducing the volume of myomatous nodes.

Nuclear factor kappa B (NF-κB) is a transcription factor that is mainly found in the cytoplasm of cells. After activation, it translocates into the nucleus and regulates the expression of numerous genes. NF-κB plays a crucial role in regulating the inflammatory response involved in the development of many malignancies and chronic diseases, including uterine fibroids [41,42]. The canonical NF-κB pathway can be triggered by innate and adaptive immune responses [27], including pro-inflammatory cytokines. In vivo studies have demonstrated that inhibition of the NF-κB pathway reduces the expression of proinflammatory cytokines such as IL-6 and IL-1b, which leads to a decrease in the size of fibroids [42]. This once again highlights the role of inflammation in the growth of uterine fibroids.

In recent years, the relationship of obesity, hypertension, hyperlipidemia, and diabetes mellitus with uterine fibroids, which develop against the background of a local and systemic inflammatory environment, has been actively studied [43]. The concept of metabolic inflammation implies a chronic mild inflammatory response to excess nutrients and energy. For example, in obesity, adipose tissue secretes various pro-inflammatory cytokines and adipokines, including leptin and adiponectin. There is evidence that an impaired adipokine profile stimulates angiogenesis and cell proliferation, as well as alters antitumor immune responses [44]. Key adipokines are involved in the pathophysiology of leiomyoma: leptin

stimulates cell proliferation and angiogenesis by suppressing apoptosis in leiomyoma cells [45], on the contrary, adiponectin exhibits anti-inflammatory and antitumor properties. A weak correlation has been established between an increase in visceral adipose tissue and the risk and size of uterine leiomyoma in women [46]. There was a significant increase in leptin levels in women with uterine fibroids, which also indicates that aberrant changes in adipokines may be associated with inflammation and the subsequent development of leiomyoma [30].

4. Conclusions

Uterine fibroids as a typical fibrotic disease are characterized by excessive accumulation of extracellular matrix in the tumor tissue. In this case, inflammation serves as a trigger mechanism that provokes the growth of clonal cells, differentiation of fibroblasts into myofibroblasts, followed by remodeling of the extracellular matrix. Increased activation and accumulation of immune cells, increased expression of many pro-inflammatory cytokines in fibroid tissue indicate an important role of inflammation in the pathogenesis of uterine fibroids. Based on this, the regulation of local inflammation in fibroids and adjacent myometrium may represent a new therapeutic strategy for the treatment of this disease.

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