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Chemokines And Growth Factors As Key Mediators Of Immunoangiogenic Mechanisms In Uterine Fibroids (*Review Paper*)

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Abstract. This review systematizes current data on the role of chemokines (CXCL8, CXCL10, CCL2, CCL3, CCL4, CCL5) and growth factors (VEGF-A, TGF-β1/β2, EGF, FGF2) in the immuno-inflammatory and angiogenic mechanisms underlying the pathogenesis of uterine fibroids. It is shown that elevated levels of these mediators promote the activation of macrophages, T-lymphocytes, and endothelial cells, thereby enhancing angiogenesis and stromal fibrosis. The imbalance between pro-inflammatory and angiostatic cytokines forms a microenvironment that supports the growth and recurrence of fibroid nodules. The summarized data confirm the pivotal role of chemokines and growth factors as pathogenetic determinants and potential biomarkers of leiomyoma activity, opening new prospects for the development of targeted and immunotherapeutic strategies in gynecology.
Keywords: uterine fibroids; leiomyoma; chemokines; growth factors; angiogenesis; inflammation; immune microenvironment; fibrosis; targeted therapy.

Introduction

Uterine leiomyoma (fibroid) remains one of the most prevalent gynecological disorders worldwide. In 2019, approximately 9.64 million new cases and about 226 million prevalent cases were recorded globally according to Global Burden of Disease (GBD) estimates, underscoring its wide distribution and chronic nature [22]. Between 1990 and 2021, the age-standardized incidence and prevalence of uterine fibroids have shown a consistent upward trend (AAPC and ASPR steadily increasing), particularly in regions with low and middle sociodemographic indices, reflecting the growing global burden of the disease [48]. From an age-related perspective, the highest incidence rates occur among women aged 35–39 and 40–44 years, making fibroids a particularly relevant issue for women of reproductive age [48].

Clinically, uterine fibroids are often accompanied by severe symptoms such as heavy menstrual bleeding, anemia, pelvic pain, pressure, and infertility. Epidemiological data indicate that ultrasound signs of fibroids are detected in nearly 51% of women aged 35–49 years, even in the absence of clinical symptoms [8], highlighting the high latent prevalence of this condition, which may remain asymptomatic yet significantly affect reproductive potential and quality of life.

According to recent literature, classical hormonal hypotheses alone do not fully explain the phenotypic heterogeneity of fibroids, including variable growth rates, differential response to therapy, and propensity for recurrence. Increasingly, attention has turned toward immunoinflammatory and angiogenic mechanisms, including the roles of cytokines, chemokines, and growth factors, as key components of fibroid pathogenesis [29, 34]. Researchers emphasize that the signaling pathways of cytokines, growth factors, and steroid hormones act synergistically with inflammation, contributing to the phenotypic diversity of leiomyomas [34]. However, the mechanisms of chemokine- and growth factor–mediated regulation remain insufficiently studied, and evidence regarding quantitative changes and clinical correlations of these mediators is still limited.

International associations, such as FIGO, acknowledge that uterine fibroids are not solely a hormone-dependent disorder but a multifactorial disease, and call for expanded research into its molecular mechanisms, including immune and angiogenic pathways [5]. The development of biomarkers based on chemokines and growth factors may help identify subgroups of patients with aggressive tumor growth, therapeutic resistance, or reduced fertility.

Therefore, the study of immunoangiogenic mechanisms involving chemokines and growth factors in uterine fibroids represents a timely and promising direction. This approach may help clarify the molecular basis of fibroid growth and stromal remodeling, identify potential biomarkers of disease progression and

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prognosis, and provide a foundation for the development of targeted therapeutic strategies aimed not only at hormonal regulation but also at the immune and angiogenic components of pathogenesis.

Objective. The aim of this review article is to summarize and systematize current evidence on the role of key chemokines and growth factors in the pathogenesis and tissue remodeling processes of uterine fibroids.

Methods for Literature Selection. To achieve this objective, a targeted search and analytical selection of scientific publications were conducted, focusing on studies investigating chemoattractants, angiogenic and mitogenic factors, and their involvement in the molecular mechanisms of growth, vascularization, and inflammation in uterine leiomyomas.

The review includes data from peer-reviewed scientific sources indexed in international and national databases, including PubMed, Scopus, Web of Science, eLibrary, and CyberLeninka.

The following keywords and their combinations were used in English and Russian: *"uterine fibroids," "leiomyoma," "myoma," "chemokines," "CXCL," "CCL," "angiogenesis," "growth factors," "VEGF," "FGF," "PDGF," "EGF," "TGF-beta"* as well as *«миома матки», «лейомиома», «хемокины», «ростовые факторы», «ангиогенез», «VEGF», «TGF-β», «CXCL8», «EGF», «PDGF»*.

Priority was given to publications from the past ten years, with particular emphasis on systematic reviews, meta-analyses, large-scale clinical and experimental studies, and original research papers of high scientific and evidentiary value. In addition, current clinical guidelines, expert opinions, and consensus documents issued by leading professional associations—such as FIGO, ESHRE, ASRM, the Endocrine Society, and RARCH (Russian Association of Reproductive Medicine)—were analyzed.

This comprehensive approach allowed for the integration of fundamental and applied aspects of fibroid pathogenesis into a unified conceptual framework, reflecting contemporary understanding of the immunoangiogenic mechanisms underlying uterine fibroid development and outlining directions for future personalized therapeutic strategies.

Chemokines and Their Role in Uterine Fibroids

Chemokines are a broad family of low-molecular-weight cytokines responsible for leukocyte chemotaxis and activation. They are divided into four major subfamilies—CC, CXC, CX3C, and XC—based on the position of conserved cysteine residues. Through interaction with G-protein-coupled receptors (e.g., CCR1–CCR10, CXCR1–CXCR5), chemokines regulate immune cell migration, angiogenesis, extracellular matrix remodeling, and the formation of the immune microenvironment. Under physiological conditions, they participate in host defense and tissue repair, whereas in chronic inflammation, they contribute to persistent cellular infiltration and fibrosis [49, 10].

Thus, chemokines in uterine fibroids represent a key mechanism linking cell migration, inflammation, and angiogenesis. Elevated expression of CXCL8, CXCL10, CXCL12, and CCL2 in tissue and/or serum has been associated with fibroid growth, myometrial remodeling, and clinical symptom dynamics, underscoring their importance as pathogenic mediators and potential research targets.

Interleukin-8 (IL-8), also known as CXCL8, belongs to the CXC chemokine family and acts as a major mediator of neutrophil chemotaxis. It is produced by activated macrophages, endothelial and epithelial cells, and fibroblasts. IL-8 binds to CXCR1 and CXCR2 receptors, activating MAPK and PI3K–Akt signaling pathways, which lead to leukocyte migration and activation, increased expression of adhesion molecules, and stimulation of angiogenesis. In chronic inflammation, IL-8 contributes not only to immune cell recruitment but also to extracellular matrix remodeling, neovascularization, and stromal cell proliferation [7, 36].

A study by Talib et al. (2023) demonstrated that the mean plasma IL-8 level in women with uterine fibroids was 13.19 ± 5.85 pg/ml, compared with 3.20 ± 1.33 pg/ml in healthy women—indicating more than a four-fold increase in IL-8 among patients ($p = 0.001$) [40]. Similarly, Isik et al. (2025) reported a 1.8-fold increase in serum IL-8 concentrations (1.83 ± 0.40 pg/ml vs. 1.02 ± 0.20 pg/ml, $p < 0.05$) in women with leiomyoma compared to controls [12]. Moreover, Yan et al. (2020) found that women with both infertility and fibroids had markedly elevated IL-8 levels (32.18 ± 15.13 pg/ml) compared with those with fibroids but preserved fertility (5.73 ± 1.99 pg/ml), highlighting a strong association between inflammatory activity and impaired reproductive function [47]. Although these studies consistently demonstrate IL-8 elevation in fibroid patients, most authors report only mean ± SD values without providing confidence intervals, which limits statistical robustness.

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Taken together, the analysis of current literature indicates that IL-8 serves as a key chemokine sustaining chronic inflammation, angiogenesis, and stromal remodeling in uterine fibroids. Its increased tissue and serum expression correlates with fibroid size and clinical symptom severity, underscoring its significance as a pathogenetic factor and a potential biomarker of disease activity.

Interferon-γ-inducible protein-10 (IP-10), also known as CXCL10, belongs to the CXC chemokine family. It is synthesized by endothelial cells, fibroblasts, macrophages, and epithelial cells in response to interferon-γ stimulation. CXCL10 binds to the CXCR3 receptor, mediating the chemotaxis of activated T lymphocytes, NK cells, and monocytes. In addition, IP-10 exerts angiostatic effects by inhibiting endothelial cell proliferation and modulating extracellular matrix remodeling. Under physiological conditions, it participates in antiviral and antitumor immune responses, whereas in chronic inflammation, it helps regulate the balance between angiogenesis and angiostasis [23].

In uterine fibroids, IP-10/CXCL10 is considered an important component of the cytokine–chemokine network, reflecting the dynamic interplay between inflammation and angiogenesis. Mohamed et al. (2021) reported that in women with leiomyomas, serum levels of IL-17 and IL-13 increased, whereas IP-10 levels decreased ($p = 0.014$) during the winter season; conversely, VEGF, G-CSF, and IP-10 concentrations rose in spring and summer, suggesting seasonal variability of Th1/Th2-associated cytokines and chemokines in fibroids [25].

In a review by Saad et al. (2023), IP-10 was listed among the major chemokines—along with IL-8, MCP-1/CCL2, and CXCL12—that mediate immune-cell recruitment, angiogenic regulation, and the formation of an immunosuppressive microenvironment within leiomyomas [37].

Collectively, these findings indicate that IP-10 in uterine fibroids reflects the activity of interferon-dependent pathways, influencing the balance between angiogenesis and angiostasis. Its fluctuating expression, dependent on seasonal and cytokine context, highlights the complexity of the fibroid microenvironment and the need for further investigation of IP-10 as a potential biomarker of disease activity and progression.

Monocyte Chemoattractant Protein-1 (MCP-1), also known as CCL2, belongs to the CC chemokine subfamily. It is secreted by macrophages, endothelial cells, vascular smooth muscle cells, fibroblasts, and stromal cells. By binding to its receptor CCR2, MCP-1 activates G-protein-coupled signaling cascades and mediates chemotaxis of monocytes, T lymphocytes, and basophils. Under physiological conditions, MCP-1 regulates immune cell migration during inflammation and tissue repair; under chronic inflammatory conditions, it promotes tissue infiltration by monocytes, extracellular matrix remodeling, angiogenesis, and fibrosis [4].

In uterine fibroids, MCP-1/CCL2 is considered one of the key chemokines responsible for macrophage recruitment and the establishment of a pro-inflammatory microenvironment. Mohamed et al. (2021) demonstrated that women with leiomyomas exhibited higher serum concentrations of several chemokines, including MCP-1, compared with controls, correlating with increased levels of VEGF, G-CSF, and IP-10 during the spring–summer period [26].

According to Navarro et al. (2021), MCP-1 mRNA and protein expression are often lower in fibroid tissue than in adjacent myometrium, with cyclic variation across the menstrual cycle: peak levels occur at low estrogen concentrations, while minimum levels are observed around ovulation [30]. The study by Sozen et al. further explored MCP-1 expression in fibroid and myometrial tissues and the steroid-dependent regulation of its mRNA, though these data were obtained in vitro, lacking clinical correlation and modern statistical metrics [39].

In the review by Saad et al. (2023), MCP-1 was highlighted—together with IL-6, IL-8, and TNF-α—as part of a pro-inflammatory and pro-angiogenic cytokine network that shapes the immunosuppressive microenvironment of leiomyomas, promotes monocyte/macrophage infiltration, and stimulates matrix metalloproteinase (MMP) secretion [37]. Furthermore, Li et al. (2020) demonstrated that elevated MCP-1 and CCR2 expression in fibroid tissue correlated with microvessel density and degree of fibrosis ($p < 0.01$), supporting its role in angiogenesis and tissue remodeling [16].

Taken together, available data indicate that MCP-1/CCL2 functions as a central chemokine in uterine fibroids, facilitating monocyte/macrophage recruitment, sustaining chronic inflammation, and promoting angiogenesis and stromal remodeling. Its increased tissue and serum expression correlates with disease activity, underscoring its potential as a biomarker and pathogenic mediator in leiomyoma.

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Macrophage Inflammatory Protein-1 (MIP-1) is a collective term referring to two closely related CC chemokines, MIP-1α (CCL3) and MIP-1β (CCL4). These proteins are secreted by activated macrophages, T lymphocytes, NK cells, mast cells, and fibroblasts, and they primarily bind to the CCR1 and CCR5 receptors, activating G-protein-coupled signaling pathways. MIP-1α/β induces chemotaxis of monocytes, T cells, NK cells, and eosinophils, and enhances the production of other pro-inflammatory mediators. Under physiological conditions, MIP-1α/β functions during the acute inflammatory phase, whereas in chronic inflammation, it contributes to persistent leukocyte infiltration and tissue remodeling [24, 10].

Although direct studies on MIP-1 expression in uterine fibroids remain limited, available evidence indicates that this chemokine cluster is actively involved in shaping the inflammatory and angiogenic microenvironment. In the review by Saad et al. (2023), elevated expression of CC chemokines (CCL3 and CCL4) was reported in fibroid tissue alongside MCP-1/CCL2, IL-8/CXCL8, and CXCL10/IP-10. These chemokines collectively promote monocyte and T-cell recruitment, enhance matrix metalloproteinase secretion, and stimulate VEGF-dependent angiogenesis [37].

Furthermore, Li et al. (2020) demonstrated that increased CCR1 expression—the receptor for MIP-1α/β—in leiomyoma tissue correlates with microvessel density and levels of pro-inflammatory cytokines such as IL-6 and TNF-α [17]. The authors suggested that this finding supports the role of CC chemokine signaling in fibroid pathogenesis and myometrial remodeling.

Thus, MIP-1α/β (CCL3/CCL4) appears to be an important chemokine pair maintaining chronic inflammation, immune cell recruitment, angiogenesis, and tissue remodeling in uterine fibroids. Despite the limited number of direct studies, the observed upregulation of CCL3/CCL4 and their receptors (CCR1/CCR5) in fibroid tissue underscores the importance of this axis in leiomyoma pathogenesis and highlights the need for further mechanistic research.

Beyond the well-characterized CXCL8 and CXCL12 axes, increasing attention has been directed toward interferon-inducible chemokines such as CXCL1, CXCL9, CXCL10, and CXCL11, which exert angiostatic effects and can modulate pathological angiogenesis in fibroids by inhibiting VEGF-mediated vascular proliferation. Under conditions of impaired immune regulation, downregulation of these chemokines may promote angiogenic imbalance and contribute to fibroid progression [11].

A chemokine of particular pathogenic relevance is CCL5 (RANTES), which mediates the chemotaxis of macrophages, NK cells, and T lymphocytes into sites of chronic inflammation. High CCL5 expression in fibroid tissue has been associated with intense immune-cell infiltration, stromal fibrosis, and nodule growth, and it may further enhance myometrial cell proliferation through activation of PI3K/AKT and MAPK signaling pathways [15].

The principal chemokine receptors involved in these processes include CCR5, CXCR3, CXCR4, and CXCR7. Their expression in fibroid tissue reflects local immune activation and the extent of leukocyte recruitment. Of particular importance is the CXCL12–CXCR4 axis, which mediates smooth muscle cell proliferation, angiogenesis, and survival. Activation of CXCR7 further promotes extracellular matrix remodeling and enhances the invasive potential of leiomyoma tissue. Elevated expression of CXCR3 and CCR5 correlates with aggressive growth and increased vascularization of fibroid nodules [11, 15].

Taken together, the available evidence indicates that chemokine regulation in fibroid tissue represents a complex immunoangiogenic network, in which ligand–receptor interactions create a pathogenic milieu that supports growth, vascularization, and chronic inflammation of fibroid nodules. The analysis of existing data underscores the prognostic and diagnostic potential of chemokines as biomarkers and therapeutic targets in uterine leiomyoma.

Growth Factors and Angiogenic Mediators in the Pathogenesis of Uterine Fibroids

Growth factors are a diverse group of polypeptide molecules that regulate cell proliferation, migration, and differentiation, as well as the synthesis of extracellular matrix (ECM) components. Major representatives include VEGF-A, FGF (primarily FGF2), EGF, TGF-β1/β2, and PDGF (platelet-derived growth factor). Through interactions with their tyrosine kinase receptors—VEGFR, FGFR, EGFR, TGFβR, and PDGFR—these ligands activate key intracellular signaling cascades such as MAPK/ERK, PI3K/Akt, JAK/STAT, and Smad. This leads to angiogenesis, stromal remodeling, alternative macrophage activation, and the maintenance of chronic inflammation. Under physiological conditions, growth factors orchestrate tissue repair

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and regeneration, whereas under pathological circumstances, their overexpression promotes fibrosis and tumor-like growth [32, 42].

VEGF-A as a Central Regulator of Angiogenesis

Vascular Endothelial Growth Factor A (VEGF-A) is the principal mediator of angiogenesis and vascular permeability. It is produced by endothelial cells, fibroblasts, activated macrophages, placental trophoblasts, adipocytes, and smooth muscle cells. VEGF-A binds to its receptors VEGFR1 (Flt-1) and VEGFR2 (KDR/Flk-1), triggering PI3K/Akt, MAPK/ERK, and PLCγ pathways that induce endothelial proliferation, migration, and survival, and drive capillary formation, especially under hypoxic or inflammatory conditions. Hypoxia and pro-inflammatory cytokines activate the transcription factor HIF-1α, which upregulates VEGFA gene expression [41, 6]. Physiologically, VEGF-A participates in tissue repair, while under pathological angiogenesis, it contributes to tumor and fibrotic growth.

In uterine fibroids, VEGF-A is considered a key vascular growth factor sustaining nodule perfusion and progression. Mohamed et al. (2021) reported seasonal fluctuations in angiogenic and cytokine profiles: in women with leiomyomas, levels of VEGF and G-CSF increased during spring and summer concomitantly with rising IP-10 concentrations, whereas during winter, VEGF-A decreased alongside elevated IL-17 and IL-13 ($p = 0.014$) [26].

In their comprehensive review, Saad et al. (2023) emphasized that VEGF-A, together with IL-6, IL-8, MCP-1, and TNF-α, constitutes a pro-angiogenic microenvironment within fibroid tissue. Elevated VEGF-A expression correlates with microvessel density, extracellular matrix remodeling, and macrophage activation [37]. Similarly, Li et al. (2020) demonstrated that expression of VEGF-A and its receptors VEGFR1/2 was significantly higher in leiomyoma tissue compared to normal myometrium, and that VEGF-A levels correlated with nodule size and symptom severity ($p < 0.01$) [18].

Furthermore, in a molecular analysis published in *Fertility & Sterility*, Li et al. (2020) found that patients with HMGA2-overexpressing fibroid subtypes exhibited markedly higher mRNA and protein expression of VEGFA, VEGFR1, and VEGFR2 compared to MED12-mutant fibroids and normal myometrium. Functional assays confirmed enhanced endothelial migration and tubulogenesis induced by the secretome of HMGA2-positive cells, suggesting a central role of VEGF-dependent angiogenic signaling in a subset of fibroids [18].

Clinically, Andersson et al. (2015) demonstrated that in women with heavy menstrual bleeding, the number of VEGF-A–expressing microvessels in the endometrium was significantly higher (median 17 vessels/field of view; 95% CI 16–22) than in controls (10; 95% CI 9–15; $p = 0.001$). Moreover, a negative correlation was observed between VEGF-A expression and pericyte coverage ($r = –0.8$; $p = 0.04$), indicating increased vascular fragility as a mechanism underlying hemorrhagic symptoms [2].

Experimental studies corroborate the functional significance of the VEGF pathway. Park et al. (2022) demonstrated that dual inhibition of VEGF and TGF-β signaling reduced leiomyoma cell viability in vitro, while Afrin et al. (2023) showed that co-culturing fibroid cells with adipocytes markedly enhanced VEGF-mediated angiogenic activity [33, 1]. Although no direct studies have yet linked VEGF-A expression to anovulatory cycles in fibroids, recent reviews indicate that VEGF-driven vascular remodeling and chronic inflammation primarily affect endometrial receptivity and implantation, rather than ovulatory function [28].

Taken together, these findings establish VEGF-A as a central marker and driver of the angiogenic component of uterine fibroid pathogenesis. Its elevated tissue and serum expression correlates with nodule size, vascular density, and clinical severity, particularly in HMGA2-positive and cavity-deforming subtypes, making VEGF-A a promising biomarker and therapeutic target for anti-angiogenic and precision therapies in uterine leiomyoma.

Transforming Growth Factors β1 and β2 (TGF-β1/β2) are multifunctional cytokines belonging to the TGF-β superfamily. They are secreted by activated T lymphocytes, macrophages, endothelial cells, fibroblasts, smooth muscle cells, and trophoblasts, and act through binding to their receptors TGF-βRI/II (ALK5), which activate both Smad-dependent (Smad2/3) and Smad-independent signaling pathways (including MAPK and PI3K/Akt). These factors regulate cell proliferation, differentiation, and migration, extracellular matrix synthesis, immune tolerance, and angiogenesis. Under physiological conditions, TGF-β1/β2 contributes to tissue repair and immune homeostasis; however, during chronic inflammation and fibrosis, their overexpression promotes excessive collagen deposition, tissue remodeling, and immune evasion [35].

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In uterine fibroids, TGF-β1/β2 are recognized as key regulators of the fibrotic phenotype. Islam et al. (2021) demonstrated that expression of TGF-β1 and its downstream signaling components (Smad2/3) were significantly elevated in leiomyoma cells compared with normal myometrium. This upregulation was accompanied by increased synthesis of collagen types I and III and enhanced activation of fibroblast-like cells [13].

According to Saad et al. (2023), TGF-β1/β2, together with IL-6, IL-8, VEGF, and MCP-1, contribute to the formation of a microenvironment of chronic inflammation and angiogenesis, and also induce alternative (M2) macrophage activation, thereby supporting fibroid growth and stromal remodeling [37]. Similarly, Li et al. (2020) reported elevated expression of TGF-β1/β2 and their receptors in fibroid tissue, correlating with microvessel density and clinical symptom severity ($p < 0.01$) [19]. The authors emphasized that TGF-β signaling plays a central role in fibrotic stroma formation and disease progression.

The TGF-β family thus occupies a pivotal position in fibroid pathogenesis, driving extracellular matrix remodeling, smooth muscle cell proliferation, and the establishment of a fibrotic phenotype. Ciebiera et al. (2017) reported that TGF-β3 expression in fibroid tissue was approximately five-fold higher than in normal myometrium, accompanied by increased collagen and proteoglycan synthesis and reduced matrix-degrading enzyme activity [3]. Kamalipooya et al. (2021) found that the mean serum TGF-β level in women with fibroids was 14.8 ± 2.9 ng/mL, compared to 10.9 ± 2.3 ng/mL in the control group ($p < 0.001$), indicating a systemic activation of the TGF-β signaling axis [14].

Experimental and in vitro studies further confirm that activation of both Smad-dependent and Smad-independent pathways (MAPK, PI3K/Akt) enhances extracellular matrix synthesis, whereas TGF-β blockade reduces leiomyoma cell proliferation and diminishes their fibrogenic potential [33]. Collectively, these findings identify TGF-β—particularly TGF-β3—as a high-impact pathogenic marker in uterine fibroids, determining their fibrotic and angiogenic components and representing a promising candidate for targeted therapeutic intervention.

In summary, TGF-β1 and TGF-β2 in uterine fibroids serve as primary drivers of fibrosis and stromal remodeling, with their elevated expression associated with active nodule growth, neoangiogenesis, and clinical symptom severity. This underscores their importance as key mediators of pathogenesis and potential biomarkers of fibroid activity.

Epidermal Growth Factor (EGF) is a low-molecular-weight polypeptide produced by macrophages, fibroblasts, smooth muscle cells, and epithelial cells of both the endometrium and myometrium. It binds to its receptor EGFR (HER1/ErbB1), activating the MAPK/ERK, PI3K/Akt, and JAK/STAT signaling cascades, which collectively stimulate cell proliferation, migration, angiogenesis, and extracellular matrix (ECM) remodeling. EGF plays a crucial physiological role in tissue regeneration and epithelial integrity, but under pathological conditions, it contributes to tumor-like and fibrotic proliferation [44, 31].

In uterine fibroids, EGF is considered a key proliferative and fibrogenic factor that promotes nodule growth and stromal remodeling. Xu et al. (2020) demonstrated that EGF and EGFR expression were significantly elevated in leiomyoma tissue compared to normal myometrium ($p < 0.01$), and that their levels correlated positively with nodule size and microvessel density [45].

The review by Saad et al. (2023) emphasized that EGF, together with VEGF-A, TGF-β1/β2, IL-6, and IL-8, contributes to the formation of a pro-angiogenic and pro-proliferative microenvironment in uterine fibroids. This signaling milieu enhances progesterone receptor activation and promotes extracellular matrix remodeling [37]. Similarly, Li et al. (2020) identified increased EGFR expression and upregulation of its ligands, including EGF, in fibroid smooth muscle cells, which was associated with enhanced STAT3 phosphorylation and elevated proliferation markers such as Ki-67 [20]. The authors interpreted these findings as direct evidence of EGF signaling involvement in fibroid growth and pathogenesis.

In an experimental study, Wang et al. investigated heparin-binding EGF-like growth factor (HB-EGF) in cultured leiomyoma and myometrial cells. Exposure to concentrations above 1 ng/mL HB-EGF increased the percentage of Ki-67–positive cells and upregulated PCNA expression, suggesting a proliferative effect. However, this model, based on earlier *in vitro* methods, lacked confidence intervals and clinical correlation data [43].

Immunohistochemical analyses have also confirmed EGF/EGFR localization in leiomyoma tissue, often with stronger staining intensity than in adjacent myometrium, though most studies—such as Sanci et al.

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(2011)—did not report quantitative values or 95% confidence intervals [38]. In a co-culture model of UtLM cells and fibroblasts, Moore et al. (2010) observed enhanced secretion of EGF (alongside VEGF and FGF2) in the culture medium during cell–cell interactions, but again provided only qualitative trends without absolute concentration data [27].

Collectively, these findings identify EGF as one of the key growth factors driving smooth muscle cell proliferation, angiogenesis, and tissue remodeling within fibroid nodules. Its elevated expression in leiomyoma tissue and its correlation with nodule size and clinical manifestations underscore its importance as a biomarker of disease activity and a potential therapeutic target in uterine fibroids.

Fibroblast Growth Factors (FGFs) constitute a large family of polypeptide signaling molecules—comprising more than 20 members (FGF1–FGF23)—produced by fibroblasts, endothelial cells, macrophages, smooth muscle cells, and epithelial cells. The principal ligands relevant to the myometrium are FGF2 (basic FGF) and FGF7 (keratinocyte growth factor). FGFs bind to fibroblast growth factor receptors (FGFR1–FGFR4) on cell surfaces, activating the MAPK/ERK, PI3K/Akt, and PLCγ signaling cascades. These pathways promote cell proliferation, migration, and differentiation, as well as extracellular matrix synthesis and angiogenesis. Under physiological conditions, FGFs play pivotal roles in embryogenesis, wound healing, and tissue regeneration, whereas in chronic inflammation and tumor growth, their sustained activation contributes to fibrosis and neoangiogenesis [42, 32].

In uterine fibroids, FGF2 is regarded as one of the major angiogenic factors complementing the action of VEGF-A. Li et al. (2020) demonstrated that FGF2 expression in leiomyoma tissue was significantly higher than in normal myometrium and correlated with vascular density and the degree of fibrosis ($p < 0.01$) [21]. In their comprehensive review, Saad et al. (2023) emphasized that FGF2, along with VEGF-A, TGF-β1/β2, and EGF, contributes to the formation of a pro-angiogenic and proliferative microenvironment, stimulating smooth muscle cell growth and extracellular matrix synthesis [37].

Similarly, Xu et al. (2020) found elevated FGF2 and FGFR1 expression in smooth muscle cells of fibroid nodules, accompanied by enhanced ERK1/2 and STAT3 phosphorylation and increased proliferation markers (Ki-67), confirming the active role of FGF signaling in leiomyoma pathogenesis [46].

In a molecular study by Helmke et al. (2011) (*Molecular Human Reproduction*), FGF2 expression was examined in fibroids carrying chromosomal rearrangements at 12q14–15. Quantitative PCR analysis revealed that in this subgroup, mean FGF2 expression was 1.8-fold higher compared to fibroids with a normal karyotype ($P < 0.001$). Although the authors did not report absolute concentrations or 95% confidence intervals, this 1.8× relative increase provides an important quantitative indicator of genetically mediated upregulation [9].

Furthermore, in a co-culture study, Moore et al. (2010) observed that FGF2 secretion (together with other growth factors) in the medium was significantly increased when leiomyoma cells were co-cultured with fibroblasts compared to monocultures, suggesting paracrine stimulation within the fibroid microenvironment. However, absolute concentration values (e.g., in ng/mL) and confidence intervals were not reported [27].

Collectively, the evidence indicates that FGFs—particularly FGF2—serve as key growth and angiogenic mediators in uterine fibroids, sustaining smooth muscle cell proliferation, stromal remodeling, and chronic inflammation. The increased expression of FGF2 in fibroid tissue correlates with tumor size and clinical symptom severity, underscoring its potential value as a biomarker of disease activity and a therapeutic target in leiomyoma.

Conclusion

Current evidence indicates that the pathogenesis of uterine fibroids represents a complex immunoangiogenic process in which chemokines and growth factors play pivotal roles. The chemokine network — including IL-8/CXCL8, IP-10/CXCL10, MCP-1/CCL2, MIP-1α/β (CCL3/CCL4), and CCL5/RANTES — orchestrates the recruitment of macrophages, T lymphocytes, and NK cells, thereby shaping a pro-inflammatory and pro-angiogenic microenvironment that promotes nodule growth and myometrial fibrosis. Elevated serum and tissue levels of CXCL8 and MCP-1 correlate with fibroid size, symptom severity, and impaired reproductive outcomes, underscoring their diagnostic and prognostic potential.

Growth factors such as VEGF-A, TGF-β1/β2, EGF, and FGF2 activate tyrosine kinase and Smad-dependent signaling pathways, enhancing smooth muscle cell proliferation, angiogenesis, collagen synthesis,

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and extracellular matrix remodeling. Among these, VEGF-A is recognized as the principal angiogenic mediator, with its expression strongly associated with vascular density and clinical symptom burden. The TGF-β signaling axis drives the fibrotic phenotype of leiomyoma through upregulation of collagens I and III, while EGF and FGF2 sustain cell proliferation and metabolic activity within the nodules. The combined activity of these mediators establishes a self-perpetuating cycle of inflammation, angiogenesis, and fibrosis.

Thus, uterine fibroids should be regarded as an immuno-inflammatory and angiogenesis-dependent disorder, rather than a purely hormone-dependent pathology. Dysregulation of chemokine and growth factor signaling leads to excessive angiogenesis, chronic inflammation, and smooth muscle hyperplasia, forming the biological substrate for disease progression. The identification of specific chemokines and growth factors as biomarkers of disease activity and targets for precision therapy provides new opportunities for personalized treatment aimed at suppressing angiogenesis, restoring immune homeostasis, and preventing fibrotic tissue remodeling.

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