Elite Journal of Medicine. Volume 2 issue 2(2024), Pp. 67-77
https://epjournals.com/journals/EJM

Unraveling the Role of Transforming Growth Factor-Beta (TGF-β) in the Progression of Fibroids

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Abstract

Fibroids, or uterine leiomyomas, represent a prevalent gynecological condition impacting women of reproductive age worldwide. Transforming Growth Factor-Beta (TGF-β) emerges as a critical mediator in the intricate landscape of fibroid development and progression. This abstract encapsulates a comprehensive review elucidating the multifaceted roles of TGF-β in the context of fibroid pathogenesis, encompassing molecular mechanisms and clinical implications. The TGF-β superfamily, comprising TGF-β isoforms (TGF-β1, TGF-β2, and TGF-β3), orchestrates diverse cellular responses governing cell proliferation, differentiation, and extracellular matrix remodeling. Dysregulated TGF-β signaling pathways contribute significantly to fibroid initiation and maintenance by promoting aberrant cellular proliferation, apoptosis resistance, and altered extracellular matrix composition within the uterine tissue. This paper consolidates current knowledge, highlighting the distinct contributions of TGF-β isoforms to fibroid pathophysiology. Enhanced TGF-β expression and downstream signaling dysregulation foster a microenvironment conducive to fibroid growth and progression. Insights into the pivotal role of TGF-β in fibroid pathogenesis open avenues for novel therapeutic modalities aimed at modulating TGF-β signaling cascades. Targeted strategies involving TGF-β inhibitors or modulation of downstream effectors hold promise for innovative treatments in fibroid management. In conclusion, this abstract provides a synopsis of the integral involvement of TGF-β in driving fibroid progression. Understanding the intricate molecular mechanisms underlying TGF-β signaling offers a foundation for novel therapeutic avenues and diagnostic advancements, fostering improved management strategies for this prevalent women's health concern. Continued research into TGF-β-mediated pathways is paramount for enhancing our understanding and clinical management of fibroids.

Citation: Obeagu EI, Obeagu GU. Unraveling the Role of Transforming Growth Factor-Beta (TGF-β) in the Progression of Fibroids. Elite Journal of Medicine, 2024; 2(2): 67-77

***Keywords**: Transforming Growth Factor-Beta (TGF-β), Fibroids, pathogenesis, fibroid growth*

Introduction

Uterine leiomyomas, commonly known as fibroids, represent one of the most prevalent benign tumors affecting women of reproductive age globally.[1] These hormonally responsive neoplasms originate from the myometrium, exhibiting diverse clinical manifestations ranging from asymptomatic cases to severe complications impacting women's health and quality of life. Despite their high incidence and clinical significance, the precise etiology and molecular mechanisms governing fibroid development remain incompletely understood.[2-6] Among the intricate network of signaling pathways implicated in fibroid pathogenesis, the Transforming Growth Factor-Beta (TGF-β) family emerges as a pivotal regulator, exerting profound influences on cellular behavior, extracellular matrix remodeling, and tissue homeostasis. The multifaceted roles of TGF-β isoforms - TGF-β1, TGF-β2, and TGF-β3 - in various physiological processes have drawn significant attention, particularly in the context of fibroid development and progression.[7]

This paper aims to dissect the intricate interplay between TGF-β signaling pathways and the pathophysiology of fibroids. By delving into the molecular mechanisms underlying TGF-β-mediated effects on cellular proliferation, apoptosis, and extracellular matrix alterations, this review seeks to elucidate how dysregulated TGF-β signaling contributes to the initiation, growth, and maintenance of fibroids.

The complexity of fibroid pathogenesis demands a comprehensive understanding of the role played by TGF-β in orchestrating the molecular events governing their development. The diverse actions of TGF-β isoforms in modulating cellular responses and their influence on the tumor microenvironment underscore the significance of exploring TGF-β as a potential therapeutic target for mitigating fibroid-associated symptoms and complications.[8] By amalgamating current knowledge and recent advancements in the field, this review endeavors to provide insights into the intricate relationship between TGF-β signaling and fibroid progression.[9] Ultimately, a thorough comprehension of TGF-β-mediated pathways within the context of fibroids may pave the way for innovative therapeutic strategies and diagnostic approaches, thus improving the management and care of individuals affected by this prevalent gynecological condition.

TGF-β Signaling Pathway

The Transforming Growth Factor-Beta (TGF-β) signaling pathway represents a complex and versatile network that plays a fundamental role in various cellular processes, including cell growth, differentiation, apoptosis, immune regulation, and extracellular matrix synthesis. This pathway consists of a cascade of signaling events that are tightly regulated and highly context-dependent.[10] The TGF-β family comprises various isoforms (TGF-β1, TGF-β2, TGF-β3), which bind to transmembrane serine/threonine kinase receptors known as TGF-β receptors type I and type II (TβRI and TβRII). Upon ligand binding, the constitutively active TβRII phosphorylates and activates TβRI.[11] Activated TβRI propagates the signal intracellularly by phosphorylating

receptor-regulated Smads (R-Smads), specifically Smad2 and Smad3. These phosphorylated R-Smads form complexes with a common partner, Smad4, forming heteromeric complexes that translocate into the nucleus.[12]

In the nucleus, the Smad complexes interact with other transcription factors, co-regulators, and DNA-binding proteins, modulating the transcriptional activity of target genes. This transcriptional regulation orchestrated by Smad complexes influences cell cycle progression, apoptosis, extracellular matrix production, and other cellular functions.[13] **MAPK (Mitogen-Activated Protein Kinase) Pathway** involves the activation of ERK, JNK, and p38 MAPKs, influencing cellular responses such as proliferation, differentiation, and apoptosis.[14] Activation of phosphatidylinositol 3-kinase (PI3K) and downstream protein kinase B (AKT) regulates cell survival, growth, and metabolism.[15] TGF-β can stimulate the RhoA GTPase, activating Rho-associated protein kinases (ROCKs) involved in cytoskeletal organization and cellular motility. The TGF-β pathway is tightly regulated by various mechanisms to maintain cellular homeostasis. Feedback loops, inhibitory Smads (Smad6 and Smad7), and other negative regulators counterbalance and fine-tune the intensity and duration of the signaling cascade.[16] Furthermore, crosstalk with other signaling pathways (e.g., Wnt, Notch, and Hedgehog) integrates TGF-β signaling into broader cellular networks, allowing for complex cellular responses and diverse functional outcomes.

Pathophysiological Implications in Fibroids

In the context of fibroids, dysregulation of the TGF-β signaling pathway can contribute to abnormal cell proliferation, increased extracellular matrix production, altered apoptosis, and disrupted tissue remodeling. Imbalances in TGF-β signaling may significantly impact the cellular microenvironment within the uterine tissue, promoting the initiation and progression of fibroids.[17] Understanding the intricate dynamics of TGF-β signaling pathways and their interplay with other cellular pathways is crucial in elucidating the molecular mechanisms underlying fibroid pathogenesis. Targeting specific components of the TGF-β pathway holds promise for innovative therapeutic interventions aimed at mitigating fibroid-associated complications and improving patient outcomes.[18]

TGF-β Isoforms and Fibroid Development

The Transforming Growth Factor-Beta (TGF-β) family comprises three major isoforms: TGF-β1, TGF-β2, and TGF-β3, each of which plays distinctive yet interconnected roles in various physiological and pathological processes, including fibroid development and progression.[19] TGF-β1 is a key isoform implicated in fibroid pathogenesis. It is involved in regulating cell growth, differentiation, and extracellular matrix (ECM) production. Increased expression of TGF-β1 has been observed in fibroid tissues, contributing to the dysregulated cell proliferation and ECM deposition characteristic of fibroids.[20] TGF-β1 stimulates fibroblasts and myofibroblasts to produce collagens, fibronectin, and other ECM components, leading to excessive matrix

deposition in fibroid nodules.[21] It also promotes the differentiation of fibroblasts into myofibroblasts, enhancing contractility and contributing to the fibrotic nature of fibroids.

TGF-β2

TGF-β2 is another isoform implicated in fibroid development, albeit with more nuanced roles compared to TGF-β1. Studies suggest that TGF-β2 might have context-dependent effects on fibroid pathogenesis.[22-23] While it shares similarities with TGF-β1 in promoting ECM synthesis and cell proliferation, its precise role in fibroid development requires further elucidation. TGF-β2, like TGF-β1, influences fibroblast activity and ECM production, potentially contributing to fibroid growth and maintenance.[24]

TGF-β3

TGF-β3, while less studied in the context of fibroids compared to TGF-β1 and TGF-β2, is known to play a role in tissue remodeling, wound healing, and cell proliferation regulation.[25] Some studies suggest that TGF-β3 may act as a counter-regulatory factor, antagonizing the effects of TGF-β1 and inhibiting excessive ECM synthesis and fibrosis.[26] Its role in balancing the actions of other TGF-β isoforms may have implications for fibroid pathophysiology, although further research is needed to delineate its precise involvement.[27]

The interplay and relative expression levels of TGF-β isoforms within the uterine tissue microenvironment are crucial determinants in fibroid development. Imbalances in the expression or signaling of these isoforms, particularly heightened TGF-β1 levels, relative to TGF-β3 or other regulatory factors, can contribute to aberrant cellular proliferation, enhanced ECM production, and altered tissue remodeling characteristic of fibroids.[28] Understanding the specific roles and interactions of TGF-β isoforms in driving fibroid pathogenesis is critical for developing targeted therapies aimed at modulating TGF-β signaling pathways and restoring the balance between isoforms.[29] Strategies targeting selective isoforms or their downstream effectors may hold promise for novel therapeutic interventions in managing fibroids and alleviating associated symptoms.

TGF-β and Fibroid Pathophysiology

The pathophysiology of fibroids, also known as uterine leiomyomas, involves a multifaceted interplay of various cellular and molecular factors, among which the Transforming Growth Factor-Beta (TGF-β) pathway holds significant relevance. TGF-β, a multifunctional cytokine, is intricately involved in the pathogenesis and progression of fibroids through its effects on cell proliferation, extracellular matrix (ECM) remodeling, apoptosis, and cellular differentiation.[30] TGF-β signaling exerts both stimulatory and inhibitory effects on cell proliferation, depending on the cellular context and the stage of fibroid development. Dysregulation of TGF-β signaling may lead to an imbalance favoring enhanced cell proliferation, contributing to the growth and expansion of fibroid nodules. TGF-β can stimulate the proliferation of fibroid cells by promoting the transition of fibroblasts to myofibroblasts and facilitating their uncontrolled growth.[31]

Altered TGF-β signaling profoundly influences ECM composition within fibroids. TGF-β isoforms, particularly TGF-β1, play a pivotal role in stimulating the synthesis and deposition of various ECM components, including collagens, fibronectin, and proteoglycans. This excessive ECM production leads to the characteristic fibrotic nature and increased stiffness observed in fibroid tissues.[32-33] TGF-β signaling also contributes to apoptosis resistance in fibroid cells. Dysregulated TGF-β signaling pathways can inhibit apoptosis, promoting cell survival and contributing to the persistence and growth of fibroid nodules.[34]

TGF-β influences cellular differentiation and phenotype, driving fibroblast differentiation into myofibroblasts, which are contractile cells involved in ECM production. This phenotypic switch may further contribute to the fibrotic nature and altered tissue architecture seen in fibroids.[35] TGF-β's involvement in tissue remodeling extends to its effects on angiogenesis within fibroid tissues. It can influence blood vessel formation and remodeling, affecting the vascularization of fibroid nodules and contributing to their growth and sustenance.[36] TGF-β also participates in regulating inflammatory responses and immune modulation within the uterine microenvironment, potentially impacting fibroid pathophysiology. Imbalances in immune cell regulation and inflammatory mediators influenced by TGF-β may contribute to fibroid growth and progression.

TGF-β as a Therapeutic Target

Transforming Growth Factor-Beta (TGF-β) has emerged as a potential therapeutic target in the context of various diseases, including fibroids (uterine leiomyomas). Given its pivotal role in regulating cell proliferation, extracellular matrix (ECM) remodeling, apoptosis, and tissue fibrosis, targeting the TGF-β signaling pathway holds promise for novel therapeutic interventions in managing fibroid-associated symptoms and controlling disease progression.[37] Small molecule inhibitors targeting the kinase activity of TGF-β receptors (TβRI and TβRII) have shown potential in preclinical studies to suppress TGF-β signaling, thereby inhibiting aberrant cell proliferation and ECM deposition associated with fibroids.[38]

Monoclonal antibodies designed to neutralize TGF-β isoforms, particularly TGF-β1, can disrupt ligand-receptor interactions, potentially attenuating TGF-β-mediated effects on fibroid growth and fibrosis. Compounds that inhibit Smad proteins involved in transducing TGF-β signaling have been investigated to interfere with downstream signaling events, modulating cellular responses and ECM synthesis in fibroid tissues.[39] Utilizing targeted drug delivery systems enables specific localization and controlled release of therapeutic agents, enhancing their efficacy while minimizing systemic side effects. Nanoparticle-based drug delivery systems or localized intrauterine drug delivery methods hold promise for delivering TGF-β inhibitors directly to fibroid tissues.[40]

Combining TGF-β inhibitors with other targeted therapies or existing treatment modalities, such as hormonal therapies or surgical interventions, may offer synergistic effects in managing fibroids. This approach could enhance therapeutic outcomes and potentially reduce the need for invasive surgical procedures.[41] Despite the therapeutic potential, several challenges exist in targeting TGF-

β for fibroid treatment. Off-target effects, dose optimization, tissue-specific delivery, and potential adverse effects on normal tissue homeostasis are critical considerations in developing TGF-β-based therapies. Furthermore, the intricate nature of TGF-β signaling and its context-dependent effects necessitate comprehensive understanding and precise targeting to achieve therapeutic efficacy.[42] Targeting the TGF-β signaling pathway holds promise as a novel therapeutic approach for managing fibroids.[43] Continued research efforts focusing on refining targeted interventions, optimizing delivery systems, and elucidating the intricate molecular mechanisms underlying TGF-β-mediated fibroid pathogenesis are imperative to advance the development of effective and safe therapeutic strategies for individuals affected by fibroids.

Clinical Implications

Understanding the role of Transforming Growth Factor-Beta (TGF-β) in fibroid pathogenesis offers prospects for personalized therapeutic strategies. Targeted interventions aimed at modulating TGF-β signaling pathways or its downstream effectors may enable tailored treatments based on individual molecular profiles, potentially improving therapeutic outcomes.[44] Exploring TGF-β as a therapeutic target opens avenues for novel treatment modalities. Combining TGF-β inhibitors with existing therapies or developing targeted drug delivery systems could enhance treatment efficacy while minimizing side effects, providing alternatives for patients intolerant to conventional treatments.[45]

Elucidating TGF-β-mediated pathways in fibroids may lead to the identification of novel biomarkers. Biomarkers indicative of TGF-β dysregulation or specific isoform expression levels could aid in early diagnosis, prognostication, and monitoring of fibroid progression, enabling timely interventions.[46] Targeting TGF-β signaling pathways might reduce the morbidity associated with fibroids, including heavy menstrual bleeding, pelvic pain, and reproductive complications. Effective therapeutic interventions could alleviate symptoms, enhancing the quality of life for affected individuals.

Future Perspectives

Advancements in understanding the intricate mechanisms of TGF-β signaling and its interplay with other pathways may pave the way for precision medicine in fibroid management. Tailored therapies based on individual patient profiles could revolutionize treatment paradigms.[47] Continued research through well-designed clinical trials is crucial to validate the efficacy and safety of TGF-β-targeted therapies in fibroid management. Translational research bridging basic science discoveries to clinical applications is essential for bringing innovative treatments to patients. Further exploration of TGF-β-mediated molecular pathways in fibroids is necessary. Unraveling the complexities of isoform-specific effects, cross-talk with other signaling pathways, and tissue-specific responses will enhance our understanding and refine targeted interventions.

Future research should prioritize patient-centered outcomes to assess treatment effectiveness, symptom relief, and impact on quality of life. Long-term studies evaluating the recurrence rates

and fertility outcomes following TGF-β-targeted therapies are essential for comprehensive evaluation. The clinical implications and future perspectives of TGF-β in fibroid management offer promising avenues for innovative treatments, personalized medicine, and improved patient care. Continued research efforts, collaborative interdisciplinary approaches, and clinical translation are pivotal in harnessing the therapeutic potential of TGF-β modulation for individuals affected by fibroids.[48-54]

Conclusion

In conclusion, the role of Transforming Growth Factor-Beta (TGF-β) in the pathogenesis and progression of fibroids (uterine leiomyomas) stands as a pivotal focal point in understanding this prevalent gynecological condition. TGF-β, with its multifaceted influence on cellular proliferation, extracellular matrix remodeling, apoptosis, and tissue fibrosis, plays a crucial role in shaping the complex microenvironment within fibroid tissues. This paper has underscored the intricate interplay of TGF-β isoforms, particularly TGF-β1, TGF-β2, and TGF-β3, in driving fibroid development and sustaining fibroid growth. Dysregulated TGF-β signaling pathways contribute significantly to the aberrant cellular responses and disrupted tissue homeostasis observed in fibroids, leading to excessive cell proliferation, altered extracellular matrix deposition, and resistance to apoptosis.

The insights gleaned from dissecting the TGF-β signaling pathway within the context of fibroids offer promising implications for clinical practice and future research endeavors. Understanding the molecular intricacies of TGF-β-mediated pathways presents opportunities for targeted therapeutic interventions aimed at modulating TGF-β signaling cascades. These interventions could potentially mitigate fibroid-associated symptoms, halt disease progression, and improve patient outcomes. The comprehensive understanding of TGF-β in fibroid pathophysiology offers a foundation for transformative advances in personalized medicine, targeted therapies, and enhanced clinical management, paving the way for improved outcomes and better quality of life for those impacted by fibroids.

References

1. AlAshqar A, Reschke L, Kirschen GW, Borahay MA. Role of inflammation in benign gynecologic disorders: from pathogenesis to novel therapies. Biology of reproduction. 2021 Jul;105(1):7-31.
2. Ifeanyi OE, Uzoma OG. A Review on Fibroid and Haptoglobin. Int. J. Curr. Res. Med. Sci. 2018;4(6):38-49.
3. Nnatuanya IN, EI O, Obeagu GU, Nnatuanya CI, Idem EE. Evaluation of Serum Haptoglobin in Fibroid Patients at Elele, Rivers State, Nigeria. Genetics. 2017;1: R7-13.
4. Ifeanyi OE, Uzoma OG. A Review on Cystatin C and Fibroid. Int. J. Curr. Res. Med. Sci. 2018;4(5):1-20.
5. Nnatuanya IN, Obeagu EI, Obeagu GU, Nnatuanya CI, Chukwudi EO. Evaluation of serum cystatin C levels in fibroid patients in Elele. Arch Med Vol. 2017(9).

Citation: Obeagu EI, Obeagu GU. Unraveling the Role of Transforming Growth Factor-Beta (TGF-β) in the Progression of Fibroids. Elite Journal of Medicine, 2024; 2(2): 67-77

6. Obeagu EI, Njar VE, Obeagu GU. Infertility: Prevalence and consequences. Int. J. Curr. Res. Chem. Pharm. Sci. 2023;10(7):43-50.
7. Zannotti A, Greco S, Pellegrino P, Giantomassi F, Delli Carpini G, Goteri G, Ciavattini A, Ciarmela P. Macrophages and immune responses in uterine fibroids. Cells. 2021;10(5):982.
8. Tal R, Segars JH. The role of angiogenic factors in fibroid pathogenesis: potential implications for future therapy. Human reproduction update. 2014;20(2):194-216.
9. Dooling LJ, Saini K, Anlaş AA, Discher DE. Tissue mechanics coevolves with fibrillar matrisomes in healthy and fibrotic tissues. Matrix Biology. 2022; 111:153-88.
10. Baba AB, Rah B, Bhat GR, Mushtaq I, Parveen S, Hassan R, Hameed Zargar M, Afroze D. Transforming growth factor-beta (TGF-β) signaling in cancer-a betrayal within. Frontiers in Pharmacology. 2022; 13:791272.
11. Tzavlaki K, Moustakas A. TGF-β Signaling. Biomolecules. 2020;10(3):487.
12. Kamato D, Burch ML, Piva TJ, Rezaei HB, Rostam MA, Xu S, Zheng W, Little PJ, Osman N. Transforming growth factor-β signalling: role and consequences of Smad linker region phosphorylation. Cellular signalling. 2013;25(10):2017-24.
13. Lakshmi SP, Reddy AT, Reddy RC. Transforming growth factor β suppresses peroxisome proliferator-activated receptor γ expression via both SMAD binding and novel TGF-β inhibitory elements. Biochemical Journal. 2017;474(9):1531-46.
14. Lei YY, Wang WJ, Mei JH, Wang CL. Mitogen-activated protein kinase signal transduction in solid tumors. Asian Pacific Journal of Cancer Prevention. 2014;15(20):8539-48.
15. Fayard E, Xue G, Parcellier A, Bozulic L, Hemmings BA. Protein kinase B (PKB/Akt), a key mediator of the PI3K signaling pathway. Phosphoinositide 3-kinase in Health and Disease: 2011; 1:31-56.
16. Sanchez-Duffhues G, Williams E, Goumans MJ, Heldin CH, Ten Dijke P. Bone morphogenetic protein receptors: Structure, function and targeting by selective small molecule kinase inhibitors. Bone. 2020; 138:115472.
17. Yang Q, Al-Hendy A. Update on the Role and Regulatory Mechanism of Extracellular Matrix in the Pathogenesis of Uterine Fibroids. International Journal of Molecular Sciences. 2023;24(6):5778.
18. El Sabeh M, Saha SK, Afrin S, Islam MS, Borahay MA. Wnt/β-catenin signaling pathway in uterine leiomyoma: role in tumor biology and targeting opportunities. Molecular and cellular biochemistry. 2021;476(9):3513-36.
19. Frangogiannis NG. Transforming growth factor–β in tissue fibrosis. Journal of Experimental Medicine. 2020;217(3).
20. Ciebiera M, Włodarczyk M, Wrzosek M, Męczekalski B, Nowicka G, Łukaszuk K, Ciebiera M, Słabuszewska-Jóźwiak A, Jakiel G. Role of transforming growth factor β in uterine fibroid biology. International Journal of Molecular Sciences. 2017;18(11):2435.
21. Islam MS, Ciavattini A, Petraglia F, Castellucci M, Ciarmela P. Extracellular matrix in uterine leiomyoma pathogenesis: a potential target for future therapeutics. Human reproduction update. 2018;24(1):59-85.

Citation: Obeagu EI, Obeagu GU. Unraveling the Role of Transforming Growth Factor-Beta (TGF-β) in the Progression of Fibroids. Elite Journal of Medicine, 2024; 2(2): 67-77

22. Afrin S, El Sabah M, Manzoor A, Miyashita-Ishiwata M, Reschke L, Borahay MA. Adipocyte coculture induces a pro-inflammatory, fibrotic, angiogenic, and proliferative microenvironment in uterine leiomyoma cells. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2023;1869(1):166564.
23. Mwaura AN, Riaz MA, Maoga JB, Mecha E, Omwandho CO, Scheiner-Bobis G, Meinhold-Heerlein I, Konrad L. Activin A Modulates Betaglycan Shedding via the ALK4-SMAD3-Dependent Pathway in Endometriotic Cells. Biomolecules. 2022;12(12):1749.
24. Tal R, Segars JH. The role of angiogenic factors in fibroid pathogenesis: potential implications for future therapy. Human reproduction update. 2014;20(2):194-216.
25. Sozen I, Arici A. Interactions of cytokines, growth factors, and the extracellular matrix in the cellular biology of uterine leiomyomata. Fertility and sterility. 2002;78(1):1-2.
26. Stolfi C, Troncone E, Marafini I, Monteleone G. Role of TGF-beta and Smad7 in gut inflammation, fibrosis and cancer. Biomolecules. 2020;11(1):17.
27. Patel B, Elguero S, Thakore S, Dahoud W, Bedaiwy M, Mesiano S. Role of nuclear progesterone receptor isoforms in uterine pathophysiology. Human reproduction update. 2015;21(2):155-73.
28. Protic O, Islam MS, Greco S, Giannubilo SR, Lamanna P, Petraglia F, Ciavattini A, Castellucci M, Hinz B, Ciarmela P. Activin A in inflammation, tissue repair, and fibrosis: possible role as inflammatory and fibrotic mediator of uterine fibroid development and growth. InSeminars in reproductive medicine 2017; 35(06): 499-509. Thieme Medical Publishers.
29. Cao T, Jiang Y, Wang Z, Zhang N, Al-Hendy A, Mamillapalli R, Kallen AN, Kodaman P, Taylor HS, Li D, Huang Y. H19 lncRNA identified as a master regulator of genes that drive uterine leiomyomas. Oncogene. 2019;38(27):5356-66.
30. Ciarmela P, Islam MS, Reis FM, Gray PC, Bloise E, Petraglia F, Vale W, Castellucci M. Growth factors and myometrium: biological effects in uterine fibroid and possible clinical implications. Human reproduction update. 2011;17(6):772-90.
31. Loomans HA, Andl CD. Intertwining of activin A and TGFβ signaling: dual roles in cancer progression and cancer cell invasion. Cancers. 2014;7(1):70-91.
32. Kirschen GW, AlAshqar A, Miyashita-Ishiwata M, Reschke L, El Sabeh M, Borahay MA. Vascular biology of uterine fibroids: connecting fibroids and vascular disorders. Reproduction. 2021;162(2): R1-8.
33. Chuang TD, Ton N, Rysling S, Quintanilla D, Boos D, Gao J, McSwiggin H, Yan W, Khorram O. The Influence of Race/Ethnicity on the Transcriptomic Landscape of Uterine Fibroids. International Journal of Molecular Sciences. 2023;24(17):13441.
34. Bhat AS, Singh NA, Rymbai E, Birendra S, Jayaram S, Selvaraj D. Importance of fibrosis in the pathogenesis of uterine leiomyoma and the promising anti-fibrotic effects of dipeptidyl peptidase-4 and fibroblast activation protein inhibitors in the treatment of uterine leiomyoma. Reproductive Sciences. 2023;30(5):1383-98.
35. Hinz B, McCulloch CA, Coelho NM. Mechanical regulation of myofibroblast phenoconversion and collagen contraction. Experimental cell research. 2019;379(1):119-28.

Citation: Obeagu EI, Obeagu GU. Unraveling the Role of Transforming Growth Factor-Beta (TGF-β) in the Progression of Fibroids. Elite Journal of Medicine, 2024; 2(2): 67-77

36. Chen JT, Wang CY, Chen MH. Curcumin inhibits TGF-β1-induced connective tissue growth factor expression through the interruption of Smad2 signaling in human gingival fibroblasts. Journal of the Formosan Medical Association. 2018;117(12):1115-23.
37. Kamalipooya S, Zarezadeh R, Latifi Z, Nouri M, Fattahi A, Salemi Z. Serum transforming growth factor β and leucine-rich α-2-glycoprotein 1 as potential biomarkers for diagnosis of uterine leiomyomas. Journal of Gynecology Obstetrics and Human Reproduction. 2021;50(3):102037.
38. Kondaiah P. Fibrogenic Factors and Molecular Mechanisms. In Oral Submucous Fibrosis: A Guide to Diagnosis and Management 2023 May 6 (pp. 159-193). Cham: Springer International Publishing.
39. Györfi AH, Matei AE, Distler JH. Targeting TGF-β signaling for the treatment of fibrosis. Matrix biology. 2018; 68:8-27.
40. Sivaraman B, Bashur CA, Ramamurthi A. Advances in biomimetic regeneration of elastic matrix structures. Drug delivery and translational research. 2012; 2:323-50.
41. Okolo S. Incidence, aetiology and epidemiology of uterine fibroids. Best practice & research Clinical obstetrics & gynaecology. 2008;22(4):571-88.
42. Ali M, Esfandyari S, Al-Hendy A. Evolving role of microRNAs in uterine fibroid pathogenesis: filling the gap! Fertility and Sterility. 2020;113(6):1167-8.
43. Lewis TD, Malik M, Britten J, Parikh T, Cox J, Catherino WH. Ulipristal acetate decreases active TGF-β3 and its canonical signaling in uterine leiomyoma via two novel mechanisms. Fertility and sterility. 2019 Apr 1;111(4):806-15.
44. Chodankar R, Critchley HO. Biomarkers in abnormal uterine bleeding. Biology of reproduction. 2019;101(6):1155-66.
45. Gungor MZ, Uysal M, Senturk S. The bright and the dark side of TGF-β signaling in hepatocellular carcinoma: mechanisms, dysregulation, and therapeutic implications. Cancers. 2022;14(4):940.
46. Kang H. Role of microRNAs in TGF-β signaling pathway-mediated pulmonary fibrosis. International journal of molecular sciences. 2017;18(12):2527.
47. Li YR, Fang Y, Lyu Z, Zhu Y, Yang L. Exploring the dynamic interplay between cancer stem cells and the tumor microenvironment: implications for novel therapeutic strategies. Journal of Translational Medicine. 2023;21(1):686.
48. AlAshqar A, Reschke L, Kirschen GW, Borahay MA. Role of inflammation in benign gynecologic disorders: from pathogenesis to novel therapies. Biology of reproduction. 2021;105(1):7-31.
49. Ifeanyi OE, Uzoma OG. A Review on Fibroid and Haptoglobin. Int. J. Curr. Res. Med. Sci. 2018;4(6):38-49.
50. Ifeanyi OE, Uzoma OG. A Review on Cystatin C and Fibroid. Int. J. Curr. Res. Med. Sci. 2018;4(5):1-20.
51. Nnatuanya IN, Obeagu EI, Obeagu GU, Nnatuanya CI, Chukwudi EO. Evaluation of serum cystatin C levels in fibroid patients in Elele. Arch Med Vol. 2017(9).
52. Nnatuanya IN, EI O, Obeagu GU, Nnatuanya CI, Idem EE. Evaluation of Serum Haptoglobin in Fibroid Patients at Elele, Rivers State, Nigeria. Genetics. 2017;1:R7-13.

Citation: Obeagu EI, Obeagu GU. Unraveling the Role of Transforming Growth Factor-Beta (TGF-β) in the Progression of Fibroids. Elite Journal of Medicine, 2024; 2(2): 67-77

53. Obeagu EI, Obeagu GU, Musiimenta E. Post partum haemorrhage among pregnant women: Update on risks factors. Int. J. Curr. Res. Med. Sci. 2023;9(2):14-7.
54. Obeagu EI, Njar VE, Obeagu GU. Infertility: Prevalence and consequences. Int. J. Curr. Res. Chem. Pharm. Sci. 2023;10(7):43-50.