REVIEW ARTICLE

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Statement of ethical aspects.

Ethical considerations: The author states that each step taken to carry out this review has been in line with the standards stipulated by the Ethics Committee of the Dr. Urquinaona Central Hospital. Likewise, he has followed the guidelines established by the World Medical Association and the 1975 Declaration of Helsinki. It should be noted that the studies considered have adopted practices that ensure integrity and respect for all participants, while complying with current regulatory standards.

Conflict of interest: The author declares that there is no conflict of interest in relation to this study. It is assured that the research and interpretation of the data were carried out impartially, without any external influence compromising the integrity of the work presented.

Funding: The author certifies that he has not received any financial support, material resources, equipment, staff, or in-kind contributions from individuals, public or private institutions for the completion of this study. He guarantees that the conclusions presented are the exclusive result of his scientific and analytical efforts.

Use of artificial intelligence: The author declares that the results and conclusions presented are based on the analysis of data collected using traditional research methods. They have not used artificial intelligence techniques, such as machine learning or natural language processing, to generate new data or formulate hypotheses, guaranteeing that the results presented are based on sound scientific principles and methodologies.

Received: 13 July 2025

Accepted: 25 August 2025

Online publication: 27 October 2025

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Cite as: Reyna-Villasmil E. SMAD2/SMAD3 as a regulatory axis in the pathogenesis and progression of endometrial cancer and their responses to hormonal therapy. Rev peru ginecol obstet. 2025;71(2). DOI: https://doi.org/10.31403/rpgo.v71i2787

SMAD2/SMAD3 as a regulatory axis in the pathogenesis and progression of endometrial cancer and their responses to hormonal therapy

SMAD2/SMAD3 como eje regulador en la patogénesis del cáncer de endometrio y la respuesta a la terapia hormonal

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DOI: https://doi.org/10.31403/rpgo.v71i2787

ABSTRACT

Endometrial cancer stands out as the most common gynecological tumor in industrialized nations. It's crucial to thoroughly understand its molecular processes, particularly in hormone-dependent cases that often exhibit treatment resistance. Research attention has focused on SMAD2/SMAD3, crucial proteins in the transforming growth factor beta signaling pathway. These proteins are fundamental for cellular development and proper functioning, encompassing proliferation and differentiation. However, their role in cancer is ambivalent: they act as tumor inhibitors in the early stages and promote invasion and metastasis in later stages. Various studies reveal that SMAD2/SMAD3 are essential for endometrial stability, and their alteration directly contributes to tumor progression. Furthermore, they interact with estrogen and progesterone, altering the response to hormonal therapies. This interaction is vital for creating new therapeutic targets and predictive biomarkers that improve the approach to endometrial cancer. The objective of this review is to analyze the role of SMAD2/SMAD3 as a regulatory axis in the pathogenesis and progression of endometrial cancer, and their influence on responses to hormonal therapy, with the aim of identifying new therapeutic targets and predictive biomarkers.

Keywords: Endometrial cancer; SMAD2; SMAD3; Hormonal therapy; Transforming growth factor beta.

RESUMEN

El cáncer de endometrio se destaca como el tumor ginecológico más común en las naciones industrializadas. Es crucial entender a fondo sus procesos moleculares, particularmente en aquellos que son hormono dependientes y suelen ser resistente al tratamiento. La atención investigadora se ha centrado en SMAD2/SMAD3, proteínas cruciales en la ruta de señalización del factor de crecimiento transformante beta. Estas proteínas son fundamentales para el desarrollo y el correcto funcionamiento celular, abarcando la proliferación y la diferenciación. No obstante, su función en el cáncer es ambivalente: funcionan como inhibidores tumorales en las primeras fases y fomentan la invasión y la metástasis en las últimas etapas. Diferentes investigaciones revelan que SMAD2/SMAD3 son esenciales para la estabilidad del endometrio, y su alteración contribuye directamente al avance del tumor. Además, interactúan con estrógeno y progesterona, alterando la respuesta a las terapias hormonales. Esta interacción es vital para crear nuevos objetivos terapéuticos y biomarcadores predictivos que mejoren el abordaje del cáncer de endometrio. El objetivo de esta revisión es analizar el papel de SMAD2/SMAD3 como eje regulador en la patogénesis y progresión del cáncer de endometrio, y su influencia en las respuestas a la terapia hormonal, con el fin de identificar nuevas dianas terapéuticas y biomarcadores predictivos.

Palabras clave: Cáncer de endometrio; SMAD2; SMAD3; Terapia hormonal; Factor de crecimiento transformante beta.

Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in industrialized nations[(1)]. It is classified as Type I (endometrioid, linked to and dependent on excess estrogen) and Type II (non-endometrioid, with less hormonal connection)[(2)]. Hormonal treatment, which influences estrogen and progesterone pathways, is essential in Type I EC; however, resistance and recurrences emphasize the importance of understanding its molecular processes[(1)].

The transforming growth factor beta (TGF-β) superfamily, together with its signaling system where SMAD proteins (SMAD2, SMAD3, and the common mediator SMAD4) act, control vital cellular processes such as cell division and specialization[3-6]. This signaling pathway is important in several diseases, including fibrosis affecting the kidneys[7]. In cancer, TGF-β/SMAD has an intricate and dual function: initially, it acts by slowing tumor growth, but later it facilitates invasion of other tissues and metastasis in more advanced stages[8].

The objective of this review is to analyze the role of SMAD2/SMAD3 as a regulatory axis in the pathogenesis and progression of endometrial cancer, and its influence on responses to hormone therapy, in order to identify new therapeutic targets and predictive biomarkers.

TGF-β/SMAD: key signaling with divergent roles and vital interactions

Canonical TGF-β/SMAD signaling begins with the binding of TGF-β ligands to their receptors, which activates the phosphorylation of SMAD2 and SMAD3. These, together with SMAD4, form complexes that translocate to the nucleus to regulate the gene expression of crucial cellular processes such as development, proliferation, and differentiation[4,6].

Despite their high sequence identity, SMAD2 and SMAD3 have distinct but overlapping functions in TGF-β signaling[6]. For example, SMAD2 is indispensable for embryonic development, unlike SMAD3[4]. A unique region in SMAD2 has been shown to allow its direct binding to DNA[9]. Their divergent roles are also observed in cell invasion (SMAD2 inhibits, SMAD3 promotes in trophoblasts) and in the induction of cell cycle arrest or apoptosis (mainly by SMAD3)[6,10].

SMAD2/SMAD3 signaling interacts complexly with other crucial and frequently dysregulated pathways in cancer, such as PI3K/AKT and MAPK[6]. Links with Ras and insulin have been identified. For example, Rac1 in pancreatic cancer modulates SMAD2/SMAD3 activation to enhance migration[11], and in breast cancer, SMAD2/SMAD3 can mediate suppressive or pro-metastatic signals depending on the context[8].

In EC, phosphatase and tensin homolog (PTEN) deficiency causes constitutive nuclear translocation of SMAD2/SMAD3, which paradoxically restricts PTEN-induced tumorigenesis[12]. In type II EC, TGF-β1 stimulates cell migration by negatively regulating PTEN via SMAD and ERK1/2. In addition, estrogen signaling (via ERα) suppresses EMT by inhibiting the TGF-β/SMAD pathway, indicating a reciprocal relationship between these pathways[13].

SMAD2/SMAD3: crucial for endometrial homeostasis and prevention of hormone-dependent cancer

Studies in normal endometrium (human and animal models) reveal that SMAD2/SMAD3 are integral components, participating in cyclical changes and hormonal response[15]. Their disruption in animal models induces hyperplasia and lethal uterine cancer, underscoring their crucial role in endometrial homeostasis and tumor suppression[14,16].

In animal models and organoids, the loss of SMAD2/SMAD3 in the uterus induces hyperplasia and cancer[14], demonstrating their key role in growth control and malignant prevention. Inhibition of SMAD2/SMAD3 in organoids alters their morphology and the expression of markers such as FOXA2 and MUC1, controlling networks essential for endometrial regeneration and differentiation, including pathways such as BMP and retinoic acid[16].

Tumor development in SMAD2/SMAD3 knockout mice is estrogen-dependent and can be prevented by early removal of the ovaries[14,17]. This suggests that SMAD2/SMAD3 counteracts the proliferative effects of estrogen in the endometrium, and its absence allows uncontrolled growth, highlighting the intimate connection between TGF-β/SMAD and the hormonal environment for normal endometrial function.

SMAD2/SMAD3 in endometrial cancer: dysfunction and dual role in tumor progression

SMAD2/SMAD3 expression and activity are altered in EC[18]. Weak or undetectable signaling of phosphorylated SMAD2 has been observed in EC[19]. However, PTEN deficiency, common in EC, induces nuclear translocation of SMAD2/SMAD3, paradoxically restricting tumorigenesis[12]. Progesterone can reduce SMAD2/SMAD3

expression in EC cells[20], although other studies report elevated SMAD3 expression in EC[21], suggesting a dual and complex role. Genomic analyses in EC have found mutations in SMAD2, SMAD3, and other genes in the TGF-β pathway in 20% of uterine tumors[16]. These mutations could alter signaling and contribute to hormonal dysregulation in the tumor microenvironment.

SMAD2/SMAD3 dysregulation in EC impacts tumor progression, affecting proliferation, apoptosis, invasion, and metastasis[18]. Loss of SMAD2/SMAD3 in mice causes hyperplasia and lethal uterine cancer[14]. In PTEN deficiency, co-ablation of PTEN and SMAD2/SMAD3 increases proliferation, suggesting that PTEN-mediated nuclear translocation of SMAD2/SMAD3 may restrict tumorigenesis[12].

SMAD2/SMAD3 and estrogen: crucial interaction in endometrial cancer

Recent evidence suggests that SMAD2/SMAD3 modulates estrogen signaling pathways in EC cells[2]. Tumor development in SMAD2/SMAD3 knockout mice is estrogen-dependent, indicating that SMAD2/SMAD3 counteracts estrogen-driven proliferation; its absence increases susceptibility to hyperplasia and malignant transformation[14].

Furthermore, SMAD3 participates in estrogen signaling in EC and breast cancer[22], suggesting its role in hormonal signaling networks. Estrogen signaling (ERα) maintains the epithelial phenotype and suppresses EMT, a process promoted by TGF-β, by inhibiting SMAD pathways[13]. This indicates a reciprocal regulatory loop between estrogen and TGF-β/SMAD. The influence of SMAD2/SMAD3 on estrogen receptor (ER) expression and activity is an active area of research[2], with emerging evidence of interaction between these pathways. Loss of the progesterone receptor (PR) in endometrial tumors is associated with resistance to hormonal treatment[23]. Since loss of SMAD2/SMAD3 can decrease PR expression[14], it is possible that SMAD2/SMAD3 influences ER through the progesterone signaling axis.

SMAD2/SMAD3 target genes are involved in estrogen-mediated responses in EC[18]. In SMAD2/SMAD3 knockout mice, lower expression of steroid biosynthesis genes is observed[24], suggesting a role for SMAD2/SMAD3 in local hormone production.

SMAD2/SMAD3: a key player in progesterone-endometrial cancer interaction

The interaction between SMAD2/SMAD3 and progesterone pathways in EC cells is an important area[1]. Progesterone antagonizes estrogen-dependent growth, and its deficiency increases the risk of EC[27]. Given the endometrial hyperproliferation in mice with SMAD2/SMAD3 loss[14], it is plausible that SMAD2/SMAD3 mediates the inhibitory effects of progesterone.

Progesterone and progestins are key treatments for EC[1]. In vitro studies show that progesterone inhibits proliferation and reduces the expression of TGF-β and SMAD2/SMAD3[20]. Furthermore, in SMAD2/SMAD3 knockout mice, hormone-dependent tumor development is associated with lower PR expression, suggesting that SMAD2/SMAD3 is essential for PR expression or signaling in tumorigenesis[14].

The influence of SMAD2/SMAD3 on PR expression and activity is of growing interest. PR status is an established prognostic marker in EC, with higher levels associated with better outcomes[2]. Stromal PR signaling is crucial for the antitumor effects of progesterone[23]. The loss of SMAD2/SMAD3 in mice reduces PR expression in the uterine tumor epithelium, suggesting its role in PR regulation during tumorigenesis[14]. Progestin therapy, a mainstay of EC treatment, acts by binding to PR[28]. Progesterone induces stromal COUP-TFII, reducing epithelial ER expression[29], which highlights the complex hormonal interaction in the endometrium and warrants investigation of the possible involvement of SMAD2/SMAD3. Although it has not been elucidated whether SMAD2/SMAD3 directly modulates PR interaction or subsequent events, its link to PR expression suggests a regulatory axis that would affect the tumor response to progesterone therapies.

In EC, the uterine tumor epithelium of SMAD2/SMAD3 knockout mice shows lower expression of steroid biosynthesis genes[24], which could affect local progesterone production. In vitro studies show that progesterone decreases the expression of SMAD2/SMAD3 and SMAD4 in EC cell lines[20], indicating a negative feedback loop. Further research on specific target genes is needed.

SMAD2/SMAD3 in endometrial cancer: a complex and promising therapeutic target

The multifaceted functions of SMAD2/SMAD3 in EC, ranging from tumor suppressor to tumor promoter[8], justify their exploration as therapeutic targets. Enhancing their suppressor functions, whose loss promotes EC in animal models, could be beneficial[14]. On the other hand, Activin B-SMAD2/SMAD3 signaling promotes aggressive behavior in type II EC (invasion and metastasis), suggesting that its inhibition would be advantageous in these tumors[30].

Several therapeutic strategies are being considered to attack the TGF-β/SMAD pathway, including ligand-receptor interaction inhibitors and SMAD2/SMAD3 activity modulators[31]. Type I TGF-β receptor inhibitors, such as SB431542, have shown promise in preclinical studies, eliminating the pro-metastatic effects of activin B in EC cells[30]. The natural compound isoliquiritigenin has demonstrated anti-metastatic effects in EC by modulating the TGF-β/SMAD pathway[32]. Other approaches include strengthening the ALK5-SMAD2/SMAD3 suppressor arm or counteracting tumor-promoting mechanisms[33].

Therapeutic targeting of TGF-β/SMAD faces challenges. Its broad role in normal tissues raises concerns about side effects[34]. Clinical trials have shown inconsistent results, possibly due to the complex and context-dependent functions of TGF-β and toxicities[31]. This underscores the need for a nuanced understanding of SMAD2/SMAD3 in EC to optimize therapy and minimize adverse effects.

SMAD2/SMAD3: potential biomarker and therapeutic target for endometrial cancer

Clinical trials in EC explore approaches to improve outcomes, including hormone therapy and targeting pathways such as phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR)[35]. Hormone therapy is key in hormone receptor-positive EC[28]. Given the modulation of hormonal responses by SMAD2/SMAD3, its influence on patient response to hormone therapy is clinically relevant.

Clinical trials are exploring combination therapies, such as progestins and mTOR inhibitors in advanced/recurrent EC[28]. A phase II trial of triple therapy (metformin, letrozole, abemaciclib) showed promising activity in recurrent EC-ER+. These findings highlight the potential of targeting multiple pathways; investigating their interaction with SMAD2/SMAD3 could optimize strategies[36]. Agents against HER2, RAS, and AKT are also being evaluated, justifying investigation of communication with SMAD2/SMAD3.

The potential of SMAD2/SMAD3 as predictive biomarkers for response to hormone therapy is promising. Given the correlation between hormonal response and ER/PR expression, and the relationship of SMAD2/SMAD3 with these receptors (especially PR), their expression or activity could serve as predictive markers[2,14]. Loss of PR is associated with a poorer response to progestin[28]. If SMAD2/SMAD3 regulate PR expression or signaling, their status in tumor samples could identify patients who would benefit most from hormone therapies.

Conclusion

SMAD2 and SMAD3 have multifaceted roles in modulating hormonal responses in the EC. Evidence highlights their intricate interaction with the estrogen and progesterone axes, crucial for disease pathogenesis and progression. They are confirmed to be essential for normal endometrial function (regeneration, differentiation), but their expression and activity are dysregulated in EC, contributing to tumor progression (proliferation, survival, invasion, and metastasis).

The dependence of tumor development on estrogen in SMAD2/SMAD3-deficient mouse models underscores their suppressive role, counteracting estrogen-mediated growth. The reciprocal influence between SMAD2/SMAD3 and progesterone receptors, and the modulation of SMAD2/SMAD3 by progesterone, illustrate a sophisticated regulatory network of hormonal responses in the healthy and neoplastic endometrium.

References

1. Zakrzewski PK. Canonical TGFβ signaling and its contribution to endometrial cancer development and progression-underestimated target of anticancer strategies. J Clin Med. 2021;10(17):3900. doi: 10.3390/jcm10173900.
2. Hanson I, Pitman KE, Edin NFJ. The Role of TGF-β3 in Radiation Response. Int J Mol Sci. 2023;24(8):7614. doi: 10.3390/ijms24087614.
3. Xiong S, Klausen C, Cheng JC, Leung PC. Activin B promotes endometrial cancer cell migration by down-regulating E-cadherin via SMAD-independent MEK-ERK1/2-SNAIL signaling. Oncotarget. 2016;7(26):40060-40072. doi: 10.18632/oncotarget.9483.
4. Frick CL, Yarka C, Nunns H, Goentoro L. Sensing relative signal in the Tgf-beta/Smad pathway. Proc Natl Acad Sci U S A. 2017;114(14):E2975-E2982. doi: 10.1073/pnas.1611428114.
5. Holtzhausen A, Golzio C, How T, Lee YH, Schiemann WP, Katsanis N, et al. Novel bone morphogenetic protein signaling through Smad2 and Smad3 to regulate cancer progression and development. FASEB J. 2014;28(3):1248-67. doi: 10.1096/fj.13-239178.
6. Kim SG, Kim HA, Jong HS, Park JH, Kim NK, Hong SH, et al. The endogenous ratio of Smad2 and Smad3 influences the cytostatic function of Smad3. Mol Biol Cell. 2005;16(10):4672-83. doi: 10.1091/mbc.e05-01-0054.
7. Liu H, Chen YG. The interplay between TGF-beta signaling and cell metabolism. Front Cell Dev Biol. 2022;10:846723. doi: 10.3389/fcell.2022.846723.
8. Chen G, Deng C, Li YP. TGF-beta and BMP signaling in osteoblast differentiation and bone formation. Int J Biol Sci. 2012;8(2):272-88. doi: 10.7150/ijbs.2929.
9. Brown KA, Ham AJ, Clark CN, Meller N, Law BK, Chytil A, et al. Identification of novel Smad2 and Smad3 associated proteins in response to TGF-beta1. J Cell Biochem. 2008;105(2):596-611. doi: 10.1002/jcb.21860.
10. Xu W, Angelis K, Danielpour D, Haddad MM, Bischof O, Campisi J, et al. Ski acts as a co-repressor with Smad2 and Smad3 to regulate the response to type beta transforming growth factor. Proc Natl Acad Sci U S A. 2000;97(11):5924-9. doi: 10.1073/pnas.090097797.
11. Huang C, Hu F, Song D, Sun X, Liu A, Wu Q, et al. EZH2-triggered methylation of SMAD3 promotes its activation and tumor metastasis. J Clin Invest. 2022;132(5):e152394. doi: 10.1172/JCI152394.
12. Millet C, Zhang YE. Roles of Smad3 in TGF-beta signaling during carcinogenesis. Crit Rev Eukaryot Gene Expr. 2007;17(4):281-93. doi: 10.1615/critreveukargeneexpr.v17.i4.30.
13. Bahia RK, Hao X, Hassam R, Cseh O, Bozek DA, Luchman HA, et al. Epigenetic and molecular coordination between HDAC2 and SMAD3-SKI regulates essential brain tumour stem cell characteristics. Nat Commun. 2023;14(1):5051. doi: 10.1038/s41467-023-40776-y.
14. Fei W, Kijima D, Hashimoto M, Hashimura M, Oguri Y, Kajita S, et al. A functional role of LEFTY during progesterone therapy for endometrial carcinoma. Cell Commun Signal. 2017;15(1):56. doi: 10.1186/s12964-017-0211-0.
15. Mhawech-Fauceglia P, Kesterson J, Wang D, Akers S, DuPont NC, Clark K, et al. Expression and clinical significance of the transforming growth factor-beta signalling pathway in endometrial cancer. Histopathology. 2011;59(1):63-72. doi: 10.1111/j.1365-2559.2011.03892.x.
16. Pompili S, Latella G, Gaudio E, Sferra R, Vetuschi A. The charming world of the extracellular matrix: A dynamic and protective network of the intestinal wall. Front Med (Lausanne). 2021;8:610189. doi: 10.3389/fmed.2021.610189.
17. Petersen M, Pardali E, van der Horst G, Cheung H, van den Hoogen C, van der Pluijm G, et al. Smad2 and Smad3 have opposing roles in breast cancer bone metastasis by differentially affecting tumor angiogenesis. Oncogene. 2010;29(9):1351-61. doi: 10.1038/onc.2009.426.
18. Zhang H, Li C, Li W, Xin W, Qin T. Research advances in adenomyosis-related signaling pathways and promising targets. Biomolecules. 2024;14(11):1402. doi: 10.3390/biom14111402.
19. Eritja N, Navaridas R, Ruiz-Mitjana A, Vidal-Sabanés M, Egea J, Encinas M, et al. Endometrial PTEN deficiency leads to SMAD2/3 nuclear translocation. Cancers (Basel). 2021;13(19):4990. doi: 10.3390/cancers13194990.
20. Kriseman ML, Tang S, Liao Z, Jiang P, Parks SE, Cope DI, et al. SMAD2/3 signaling in the uterine epithelium controls endometrial cell homeostasis and regeneration. Commun Biol. 2023;6(1):261. doi: 10.1038/s42003-023-04619-2.
21. Monsivais D, Peng J, Kang Y, Matzuk MM. Activin-like kinase 5 (ALK5) inactivation in the mouse uterus results in metastatic endometrial carcinoma. Proc Natl Acad Sci U S A. 2019;116(9):3883-3892. doi: 10.1073/pnas.1806838116.1.
22. Ruiz-Mitjana A, Navaridas R, Vidal-Sabanés M, Perramon-Güell A, Yeramian A, Felip I, et al. Lack of extracellular matrix switches TGF-β induced apoptosis of endometrial cells to epithelial to mesenchymal transition. Sci Rep. 2022;12(1):14821. doi: 10.1038/s41598-022-18976-1.
23. Xiong S, Klausen C, Cheng JC, Zhu H, Leung PC. Activin B induces human endometrial cancer cell adhesion, migration and invasion by up-regulating integrin β3 via SMAD2/3 signaling. Oncotarget. 2015;6(31):31659-73. doi: 10.18632/oncotarget.5229.
24. Yang J, Wahdan-Alaswad R, Danielpour D. Critical role of Smad2 in tumor suppression and transforming growth factor-beta-induced apoptosis of prostate epithelial cells. Cancer Res. 2009;69(6):2185-90. doi: 10.1158/0008-5472.CAN-08-3961.
25. Perevalova AM, Kobelev VS, Sisakyan VG, Gulyaeva LF, Pustylnyak VO. Role of tumor suppressor PTEN and its regulation in malignant transformation of endometrium. Biochemistry (Mosc). 2022;87(11):1310-1326. doi: 10.1134/S0006297922110104.
26. Piestrzeniewicz-Ulanska D, Brys M, Semczuk A, Rechberger T, Jakowicki JA, Krajewska WM. TGF-beta signaling is disrupted in endometrioid-type endometrial carcinomas. Gynecol Oncol. 2004;95(1):173-80. doi: 10.1016/j.ygyno.2004.06.032.
27. Mazerbourg S, Klein C, Roh J, Kaivo-Oja N, Mottershead DG, Korchynskyi O, et al. Growth differentiation factor-9 signaling is mediated by the type I receptor, activin receptor-like kinase 5. Mol Endocrinol. 2004;18(3):653-65. doi: 10.1210/me.2003-0393.

28. Xiong S, Cheng JC, Klausen C, Zhao J, Leung PC. TGF-β1 stimulates migration of type II endometrial cancer cells by down-regulating PTEN via activation of SMAD and ERK1/2 signaling pathways. Oncotarget. 2016;7(38):61262-61272. doi: 10.18632/oncotarget.11311.

29. Yoon SH, Lee S, Kim HS, Song J, Baek M, Ryu S, et al. NSDHL contributes to breast cancer stem-like cell maintenance and tumor-initiating capacity through TGF-beta/Smad signaling pathway in MCF-7 tumor spheroid. BMC Cancer. 2024;24(1):1370. doi: 10.1186/s12885-024-13143-3.

30. Bokhari AA, Lee LR, Raboteau D, Hamilton CA, Maxwell GL, Rodriguez GC, et al. Progesterone inhibits endometrial cancer invasiveness by inhibiting the TGFbeta pathway. Cancer Prev Res (Phila). 2014;7(10):1045-55. doi: 10.1158/1940-6207.CAPR-14-0054.

31. Wu F, Yang J, Liu J, Wang Y, Mu J, Zeng Q, et al. Signaling pathways in cancer-associated fibroblasts and targeted therapy for cancer. Signal Transduct Target Ther. 2021;6(1):218. doi: 10.1038/s41392-021-00641-0.

32. De P, Aske JC, Dale A, Rojas Espaillat L, Starks D, Dey N. Addressing activation of WNT beta-catenin pathway in diverse landscape of endometrial carcinogenesis. Am J Transl Res. 2021;13(11):12168-12180.

33. Baxter E, Windloch K, Kelly G, Lee JS, Gannon F, Brennan DJ. Molecular basis of distinct oestrogen responses in endometrial and breast cancer. Endocr Relat Cancer. 2019;26(1):31-46. doi: 10.1530/ERC-17-0563.

34. Yi M, Li T, Niu M, Zhang H, Wu Y, Wu K, et al. Targeting cytokine and chemokine signaling pathways for cancer therapy. Signal Transduct Target Ther. 2024;9(1):176. doi: 10.1038/s41392-024-01868-3.

35. Tian T, Fu X, Hu L, Yang X, Sun P, Sun F. FAST1 predicts poor survival of renal carcinoma and promotes its progression through the TGF-β/Smad pathway. Onco Targets Ther. 2021;14:1487-1499. doi: 10.2147/OTT.S288847.

36. Xie H, Li M, Zheng Y. Associations of metformin therapy treatment with endometrial cancer risk and prognosis: A systematic review and meta-analysis. Gynecol Oncol. 2024;182:15-23. doi: 10.1016/j.ygyno.2024.01.007.