Sex Hormones and mTOR Signaling: Mechanisms, Metabolic Crosstalk, and Clinical Implications

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Introduction

mTOR is a vital protein kinase enzyme that serves as the central control panel for human cell growth, metabolism, and survival by sensing nutrient availability, energy levels, and cellular stress. mTOR integrates signals from nutrients, growth factors, and energy status to coordinate anabolic and catabolic processes throughout the body. Over the past two decades, growing evidence has established that sex hormones — including estrogens, androgens, and progesterone — engage in extensive crosstalk with mTOR signaling pathways. This bidirectional relationship has profound consequences for reproductive health, metabolism, longevity, and disease susceptibility.

Understanding how sex hormones modulate mTOR activity — and how mTOR in turn influences hormone synthesis and action — is clinically essential. Dysregulation of this axis underlies several prevalent conditions, notably polycystic ovary syndrome (PMOS) and the metabolic changes commonly associated with menopause. This article provides an overview of the key molecular mechanisms, physiological consequences, and clinical implications of sex hormone-mTOR interactions.

mTOR: Signaling Architecture and Function

The Two mTOR Complexes

mTOR doesn't work alone; it functions as part of two different protein teams, called mTORC1 and mTORC2, each with a different job. Each complex has unique scaffold proteins, upstream regulators, and downstream effectors.

When mTORC1 is turned on, it:

- Increases protein production
- Stimulates cell growth and repair
- Promotes ribosome production
- Blocks autophagy, the cell's recycling process

When mTORC1 is turned off, the cell shifts into a conservation mode:

- Protein production slows
- Cell growth decreases
- Autophagy is activated so the cell can recycle damaged components and generate energy

Because mTORC1 promotes growth, it is highly sensitive to nutrient availability, especially amino acids.

mTORC2 has a different role. Instead of directly controlling growth, it helps cells:

- Survive stress
- Maintain their structure and shape
- Respond to hormones such as insulin
- Fully activate the important signaling protein Akt, which supports cell survival and metabolism

Upstream Regulation of mTORC1

mTORC1 acts like a decision-making hub that needs multiple “green lights” before allowing growth. It becomes active only when the cell has:

- Enough amino acids (especially leucine)
- Growth signals such as insulin or IGF-1
- Adequate energy (ATP)

If these signals are present, a small protein called Rheb switches mTORC1 on. When energy is low, the cell activates AMPK, its energy sensor.

AMPK tells mTORC1 to slow down by activating the TSC1/TSC2 complex, which switches off Rheb. As a result:

- Cell growth slows
- Protein synthesis decreases
- Autophagy increases to recycle cellular materials and conserve energy

mTORC1 promotes growth when nutrients and energy are abundant, while AMPK helps the cell conserve resources when energy is scarce. This balance allows cells to grow only when conditions are favorable.

Sex Hormones: Biosynthesis and Receptors

Sex hormones are steroid derivatives synthesized primarily in the gonads and adrenal cortex from cholesterol. The principal classes are estrogens (estradiol, estrone, estriol), androgens (testosterone, dihydrotestosterone, DHEA), and progestogens (progesterone). Their effects are mediated through nuclear receptors — estrogen receptors ERα and ERβ, androgen receptor (AR), and progesterone receptor (PR) — as well as through non-genomic membrane-associated receptors that trigger rapid cytoplasmic signaling cascades.

Critically, sex hormone receptors do not operate in transcriptional isolation. They physically interact with or transcriptionally regulate components of the PI3K-Akt-mTOR pathway, creating a direct molecular bridge between hormonal and metabolic signaling, there is a lot of crosstalk going on.

Molecular Mechanisms of Sex Hormone–mTOR Crosstalk

Estrogen and mTOR

Estradiol activates mTORC1 through multiple mechanisms. Via ERα, estradiol stimulates PI3K activity, leading to Akt phosphorylation and subsequent inhibition of TSC2. This pathway is operative in breast epithelium, bone, and the hypothalamus. In the liver, estrogen promotes insulin sensitivity partly by facilitating appropriate mTORC1 activity and suppressing hepatic gluconeogenesis.

Conversely, mTORC1 activation through S6K1 can phosphorylate and activate ERα in a ligand-independent manner, providing a mechanism by which growth factor signals can mimic estrogenic effects. This crosstalk has important implications for hormone receptor-positive breast cancers, where mTOR inhibition with everolimus is used to overcome endocrine resistance.

Estrogen also exerts anti-inflammatory and mitochondrial protective effects, in part through modulating mTORC1-driven protein synthesis and enhancing autophagy. Loss of estrogen at menopause disrupts this balance, contributing to increased oxidative stress and metabolic dysfunction.

Androgens and mTOR

Testosterone and its potent metabolite dihydrotestosterone (DHT) robustly activate mTORC1 signaling in muscle, liver, and adipose tissue. In skeletal muscle, androgen-mediated mTORC1 activation promotes protein synthesis and hypertrophy — a mechanism underlying the anabolic effects of testosterone. The AR directly upregulates expression of insulin receptor substrate-1 (IRS-1), amplifying PI3K-Akt-mTOR responsiveness to insulin.

However, androgen excess creates a pathological mTOR hyperactivation state. Chronically elevated androgens, as seen in PMOS, drive excessive mTORC1 activity in ovarian theca cells, promoting androgen biosynthesis in a self-reinforcing loop. In adipose tissue, androgen-driven mTORC1 activation impairs the normal transition between lipogenesis and lipolysis, contributing to central fat deposition and insulin resistance.

Progesterone and mTOR

Progesterone's relationship with mTOR is more context-dependent. In the uterus, progesterone signaling through PR activates mTORC1 to support endometrial decidualization and implantation. During early placental development, mTORC1 acts as a nutrient sensor that coordinates trophoblast invasion with maternal metabolic status — a process sensitive to progesterone levels.

In the brain, progesterone metabolites (neurosteroids) can modulate mTOR indirectly through GABA-A receptor activation and neuroprotective pathways. These effects may be relevant to cognitive and mood changes associated with hormonal fluctuations across the menstrual cycle and menopause.

Clinical Implications: Polyendocrine Metabolic Ovarian Syndrome (PMOS, formerly PCOS)

Pathophysiology

PMOS is the most common endocrine disorder in women of reproductive age, affecting 8–13% of this population worldwide. Its hallmarks are hyperandrogenism, oligo-ovulation or anovulation, and polycystic ovarian morphology. Insulin resistance is present in approximately 70% of affected women, even in the absence of obesity, and plays a central mechanistic role.

High insulin levels overstimulate certain signals inside the ovaries (a pathway called PI3K-Akt-mTORC1), which boosts androgen production even more. At the same time, this same overactive pathway blocks insulin from doing its normal job of managing blood sugar — but strangely, it doesn't block insulin's effect on androgen production. The result is a repeating cycle: high insulin → high androgens → irregular ovulation → and the cycle continues

> **Clinical Pearl: Berberine as a Botanical mTOR Modulator in PMOS**
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> *Berberine, an isoquinoline alkaloid derived from Berberis species (barberry, goldenseal), potently activates AMPK via inhibition of mitochondrial Complex I, which increases the AMP:ATP ratio and triggers AMPK-mediated phosphorylation and activation of TSC2. This indirectly suppresses mTORC1 and the downstream S6K1-IRS-1 inhibitory serine phosphorylation loop that underlies selective insulin resistance in PMOS.*
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> *Multiple randomized controlled trials demonstrate that berberine (500 mg three times daily) reduces fasting insulin, lowers serum LH:FSH ratio, decreases androgen levels, and restores ovulatory frequency in women with PMOS — with effect sizes comparable to those reported for conventional pharmacological insulin sensitizers in similar populations.*
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> *Additionally, berberine exhibits direct anti-androgenic activity in theca cells by suppressing CYP17A1 expression, further dampening the androgen-mTORC1 feedforward loop. Berberine should be taken with meals to reduce GI side effects and should be used with caution in pregnancy.*

> **Clinical Pearl: Inositol, N-Acetylcysteine, and Alpha-Lipoic Acid in PMOS**
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> *A complementary botanical and nutraceutical strategy targets mTORC1 dysregulation through multiple upstream nodes.*
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> - *Myo-inositol (4 g/day) and D-chiro-inositol (100 mg/day) at the physiological 40:1 plasma ratio function as insulin second messengers that enhance PI3K-Akt signaling fidelity, normalizing mTORC1 activity in ovarian tissue without inducing systemic hyperactivation. Meta-analyses confirm improvements in oocyte quality, androgen levels, and menstrual cyclicity.*
> - *N-acetylcysteine (NAC, 1.8 g/day), a glutathione precursor, reduces reactive oxygen species that otherwise impair IRS-1 tyrosine phosphorylation and mTOR complex integrity; clinical trials show NAC improves insulin sensitivity and ovulation rates in PMOS comparably to inositol preparations in some cohorts.*

> • *Alpha-lipoic acid (ALA, 600 mg/day) acts as a dual antioxidant and AMPK activator, with studies demonstrating reductions in fasting insulin, androgen concentrations, and inflammatory cytokines that drive mTOR hyperactivation.*
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> *Clinical tip: combining myo-inositol with ALA and vitamin D (targeting serum 25-OH-D of 40–60 ng/mL, since vitamin D receptor signaling augments PI3K efficiency) addresses three distinct nodes of the mTOR dysregulation cascade simultaneously and is well-tolerated as a first-line nutraceutical protocol.*

Clinical Implications: Postmenopausal Health

mTOR Dysregulation After Estrogen Loss

The menopausal transition is characterized by a precipitous decline in ovarian estradiol production. Because estrogen normally modulates mTOR activity in a tissue-specific manner, promoting appropriate anabolism in bone and muscle while restraining excessive mTORC1 activity in adipose tissue and the vasculature, estrogen withdrawal disrupts this balance simultaneously across multiple organ systems.

In bone, reduced PI3K-Akt-mTOR signaling in osteoblasts decreases bone formation while RANKL-mediated osteoclast activation increases resorption, culminating in postmenopausal osteoporosis. In skeletal muscle, estrogen loss diminishes mTORC1 responsiveness to protein intake, contributing to sarcopenia. In visceral adipose tissue, unopposed androgen effects and dysregulated mTORC1 promote lipid accumulation and adipose inflammation, elevating cardiovascular risk.

Additionally, aging itself progressively impairs upstream mTOR regulation. The combination of estrogen loss and age-related mTOR dysregulation creates a compounded metabolic vulnerability in postmenopausal women that manifests as accelerated cardiometabolic risk, bone loss, cognitive decline, and reduced longevity.

> **Clinical Pearl: Exercise as mTOR Optimization in Postmenopausal Women**
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> *Resistance exercise is the most potent non-pharmacological activator of skeletal muscle mTORC1 signaling and remains effective even in the absence of estrogen. Post-exercise mTORC1 activation peaks 1–2 hours after training and synergizes with adequate leucine-rich protein intake. Postmenopausal women require approximately 1.2–1.6 g/kg/day of high-quality protein, higher than pre-menopausal recommendations, because estrogen loss blunts the anabolic sensitivity of muscle mTORC1 to protein stimulation.*

> **Clinical Pearl: Menopausal Hormone Therapy and mTOR-Mediated Bone Protection**
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> *Hormone therapy (HT) with estradiol preserves bone mineral density by maintaining estrogen-driven PI3K-Akt-mTOR signaling in osteoblasts, which promotes osteoblast survival and bone matrix synthesis. The Women's Health Initiative Bone Study confirmed that standard-dose HT reduces fracture risk by 24–33%. However, the timing hypothesis (also called the "critical window") is mechanistically relevant if oral estrogen is used.* ***Review the Kajarin newsletter on hormone receptor activation after the 10 year window post menopause.***

Summary and Future Directions

The interplay between sex hormones and mTOR signaling represents a fundamental axis of metabolic regulation. Estrogens, androgens, and progesterone each engage the PI3K-Akt-mTOR pathway in tissue-specific ways, and disruption of this crosstalk contributes to the pathophysiology of PMOS, postmenopausal metabolic syndrome, and age-related chronic disease.

Clinically, targeting the sex hormone–mTOR interface offers tangible therapeutic opportunities: botanical AMPK activators such as berberine and nutraceutical insulin sensitizers including inositol, NAC, and alpha-lipoic acid in PMOS, and exercise-protein synergy with progesterone and estrogen therapy in post menopausal women.

References

1. Laplante M, Sabatini DM. mTOR signaling in growth control and disease. Cell. 2012;149(2):274-293. doi:10.1016/j.cell.2012.03.017
2. Gonzalez A, Hall MN, Lin SC, Hardie DG. AMPK and TOR: the Yin and Yang of cellular nutrient sensing and growth control. Cell Metab. 2020;31(3):472-492. doi:10.1016/j.cmet.2020.01.015
3. Teede HJ, Tay CT, Laven JJE, et al. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. J Clin Endocrinol Metab. 2023;108(10):2447-2469. doi:10.1210/clinem/dgad463
4. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev. 1997;18(6):774-800. doi:10.1210/edrv.18.6.0318
5. Unfer V, Carlomagno G, Dante G, Facchinetti F. Effects of myo-inositol in women with PMOS: a systematic review of randomized controlled trials. Gynecol Endocrinol. 2012;28(7):509-515. doi:10.3109/09513590.2011.650660
6. Tang LQ, Wei W, Chen LM, Liu S. Effects of berberine on diabetes induced by alloxan and a high-fat/high-cholesterol diet in rats. J Ethnopharmacol. 2006;108(1):109-115. doi:10.1016/j.jep.2006.04.021
7. An Y, Sun Z, Zhang Y, Liu B, Guan Y, Lu M. The use of berberine for women with polycystic ovary syndrome undergoing IVF treatment. Clin Endocrinol. 2014;80(3):425-431. doi:10.1111/cen.12294
8. Fulghesu AM, Ciampelli M, Muzj G, et al. N-acetyl-cysteine treatment improves insulin sensitivity in women with polycystic ovary syndrome. Fertil Steril. 2002;77(6):1128-1135. doi:10.1016/s0015-0282(02)03133-3
9. Genazzani AD, Shefer K, Della Casa D, et al. Modulatory effects of alpha-lipoic acid (ALA) administration on insulin sensitivity in obese PMOS patients. J Endocrinol Invest. 2018;41(5):583-590. doi:10.1007/s40618-017-0782-z
10. Hammes SR, Levin ER. Impact of estrogens in males and androgens in females. J Clin Invest. 2019;129(5):1818-1826. doi:10.1172/JCI125194
11. Harrington LS, Findlay GM, Gray A, et al. The TSC1-2 tumor suppressor controls insulin-PI3K signaling via regulation of IRS proteins. J Cell Biol. 2004;166(2):213-223. doi:10.1083/jcb.200403069
12. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA. 2003;290(13):1729-1738. doi:10.1001/jama.290.13.1729
13. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-333. doi:10.1001/jama.288.3.321
14. Bhasin S, Apovian CM, Travison TG, et al. Effect of protein intake on lean body mass in functionally limited older men: a randomized clinical trial. JAMA Intern Med. 2018;178(4):530-541. doi:10.1001/jamainternmed.2018.0008
15. Mannick JB, Del Giudice G, Lattanzi M, et al. mTOR inhibition improves immune function in the elderly. Sci Transl Med. 2014;6(268):268ra179. doi:10.1126/scitranslmed.3009892
16. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(11):3975-4011. doi:10.1210/jc.2015-2236