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• The lifetime incidence of leiomyomas ranges from 50-80%.

• Total annual cost (both direct and indirect) in the US is estimated to be $34.4 billion.
Types of Fibroids

- Pedunculated fibroid
- Intracavitary fibroid
- Subserosal fibroid
- Submucosal fibroid
- Intramural fibroid
- Fallopian tube
- Ovary
- Uterus
- Cervix
- Vagina
Proposed regulation of the growth factors and apoptosis-related factors in uterine leiomyoma cells by sex steroid hormones.

Nuclear receptors

Estrogen receptors classified into nuclear and plasma membrane-bound.

Nuclear; While ERα is mainly expressed in uterus and breast, ERβ is more broadly distributed in ovary, brain, bone, and other organs. However, both ERα and ERβ are co-expressed in several organs.
Membrane-bound receptors

- Membrane-bound estrogen receptors include the same nuclear estrogen receptors localized to the plasma membrane (mERs) and unique ones such as the more recently identified G protein-coupled receptor 30 (GPR30).

Both α and β subtypes are localized at the plasma membrane (known as mERα and mERβ).
Normal regulation of survival/apoptosis balance in uterine leiomyoma
2- methoxyestradiol

• Estrogen metabolite 2- methoxyestradiol induces apoptosis and inhibits cell proliferation and collagen production in rat and human leiomyoma cells: a potential medicinal treatment for uterine fibroids.

2- methoxyestradiol

- Catechol-o-methyltransferase expression and 2- methoxyestradiol affect microtubule dynamics and modify steroid receptor signaling in leiomyoma cells.

TGF-β3

• 2-methoxyestradiol (an estrogen metabolite with anti-tumor properties) inhibits TGF-β3 profibrotic effects in leiomyoma cells through Smad and non-Smad mediated pathways.

TGF-β3

• Furthermore, De Falco and colleagues used tissues obtained from hysterectomy patients and demonstrated that TGF-β3 and connective tissue growth factor are overexpressed in leiomyoma compared to myometrium.

TGF-β3

• Leiomyoma tissue overexpress TGF-β3 compared to myometrial tissue.

Progesterone signaling as a therapeutic target in leiomyoma treatment

• Randomized 42 women with symptomatic uterine fibroids into treatment with progesterone antagonist mifepristone or placebo for 26 weeks.

• They found that mifepristone treatment was associated with a significant tumor size reduction, improvement of anemia, and improved subjective assessment of quality of life
Mifepristone

• The same group followed patients for 12 months and confirmed tumor shrinkage. However, they found modest increase in endometrial hyperplasia.

Asoprisnil

• Induction of apoptotic signaling pathways and inhibition of proliferative signaling pathways. Importantly, these changes were noted in leiomyoma but not myometrial cells.

Growth Factors

• Modulating PI3K/Akt/mTOR pathway seems to be an intriguing target in leiomyoma therapy.

• Akt inhibition by MK-2206, an investigational drug currently in phase II trials, inhibits leiomyoma growth and induces cellular death. In addition, there is a published patent to use an mTOR inhibitor as a treatment of leiomyoma.

Growth Factor

- Growth factor binding to the RTK leads to receptor dimerization and autophosphorylation. This leads to downstream activation of several pathways including Grb2-Sos-Ras-Raf-MEK-ERK and PI3K-PIP3-Akt.
Wnt/beta-catenin

• Estrogen and progesterone-induced proliferation is leiomyomas is modulated, at least in part, through Wnt expression by mature leiomyoma cells and its paracrine response on beta catenin signaling in leiomyoma side-population (LMSP).

Network analysis of key genes involved in leiomyosarcoma development

"Sarcomagenesis signature"
Genes most over- and under-expressed in uterine leiomyosarcoma

Upregulated
- Oncogenes
- Proteinases
- Cell cycle regulation
- Cell homeostasis
- Cell structure

Downregulated
- Oncogenes
- Signal transduction
- Metabolism
- Cell cycle regulation
- Cell cycle and structure
- Cell homeostasis

Serotonin induces aromatase activity.
Aromatase

• Expression of the CYP19 gene and its product aromatase cytochrome P450 in human uterine leiomyoma tissues and cells in culture.

Aromatase Inhibitors

- Aromatase inhibitors decreased the size of the fibroids

Letrozole

• Three months treatment significantly decreased the size of fibroids without osteroporosis
5-HT receptor-mediated signaling pathways


Hocam, mekanizma hakkında çok detay vermemek için isterseniz bu slaytı çıkarabilirim!
Chemical structure of SB216641

**SB216641**; A selective 5-HT receptor antagonist.
Does SB216641, a selective antagonist of 5-HT receptors, have any therapeutic potential through proliferation and cell death in uterine fibroid cells?
huLM cells were incubated without or with SB216641, 1, 2, 3, 4, 5μM, for 14 days. The colonies were visualized by crystal violet dye.
huLM cells were treated without or with 2, 4, 6, 8, 10 μM doses of SB216641 for 72h. *p<0.05 vs. untreated condition.

SB216641 inhibits the cell viability in a dose dependent manner in huLM cells.
SB216641 induces PARP cleavage and autophagosome formation in huLM cells.

huLM cells were incubated without or with 5 or 10 μM SB216641 for 6h, 24h and 48h.
SB216641 induces PARP cleavage and autophagosome formation in huLM cells