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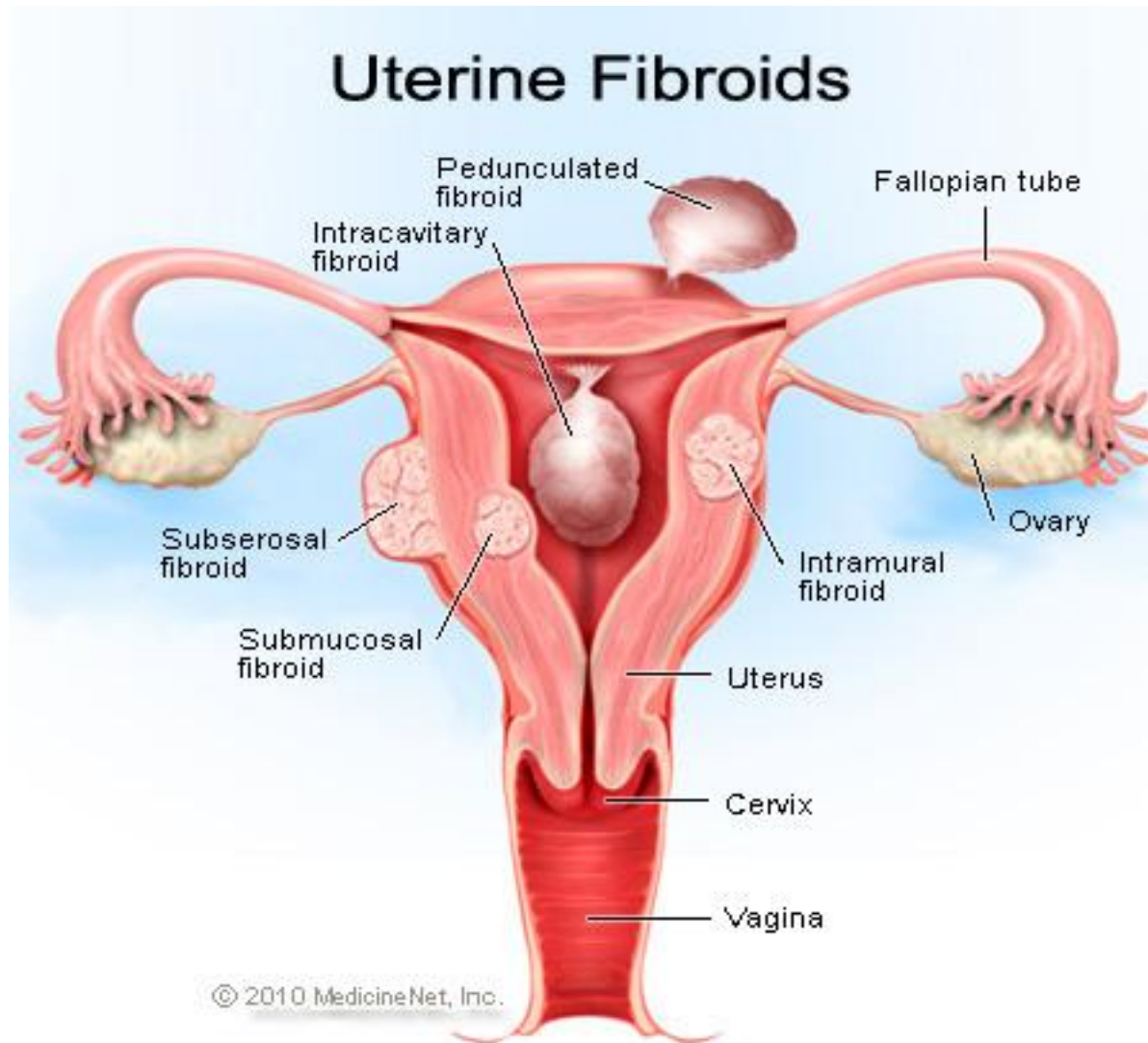
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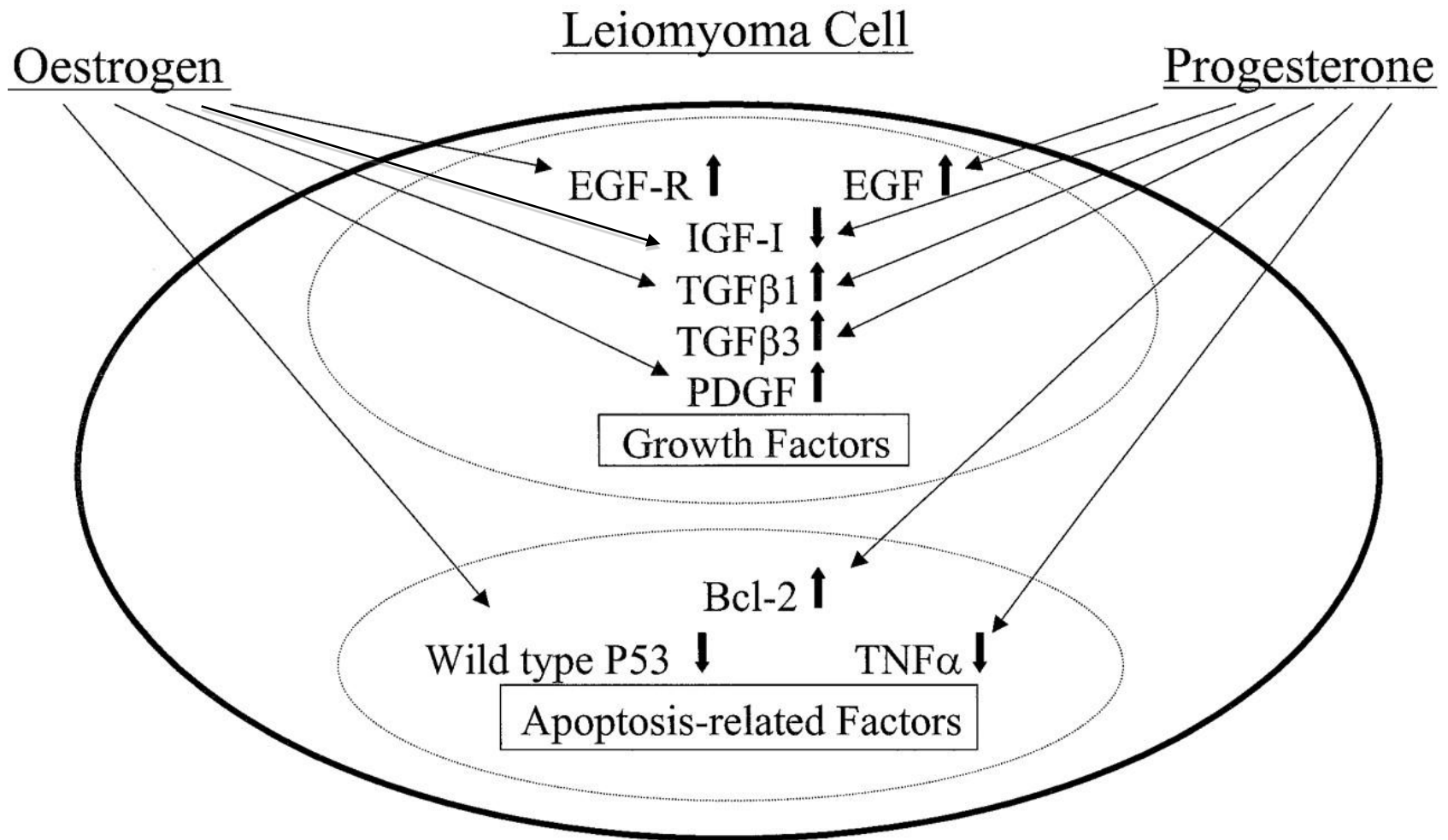
April 24, 2014

- 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



Proposed regulation of the growth factors and apoptosis-related factors in uterine leiomyoma cells by sex steroid hormones.



Nuclear receptors

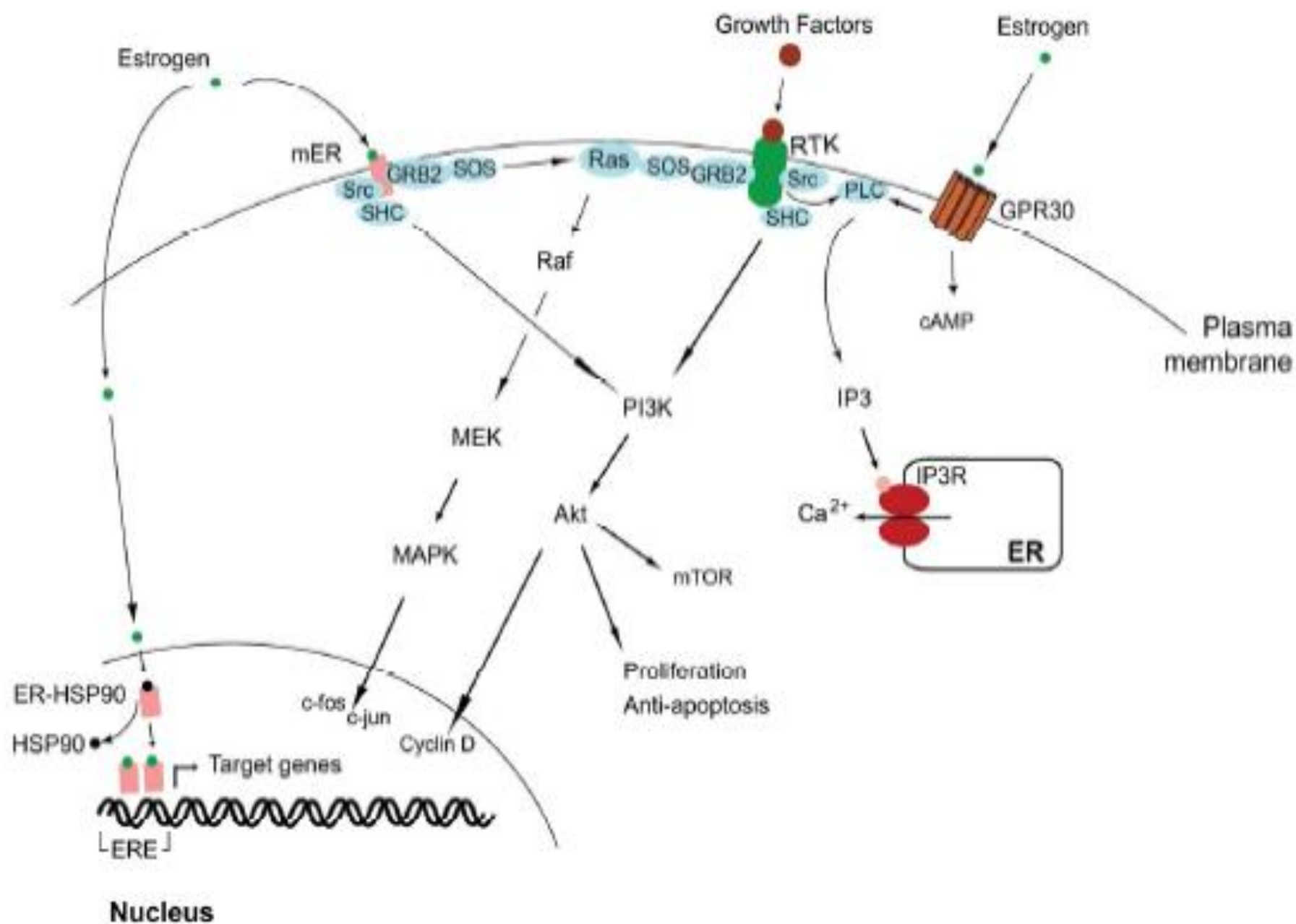
Estrogen receptors classified into nuclear and plasma membrane-bound.

Nuclear; While ER α is mainly expressed in uterus and breast, ER β is more broadly distributed in ovary, brain, bone, and other organs. However, both ER α and ER β are co-expressed in several organs.

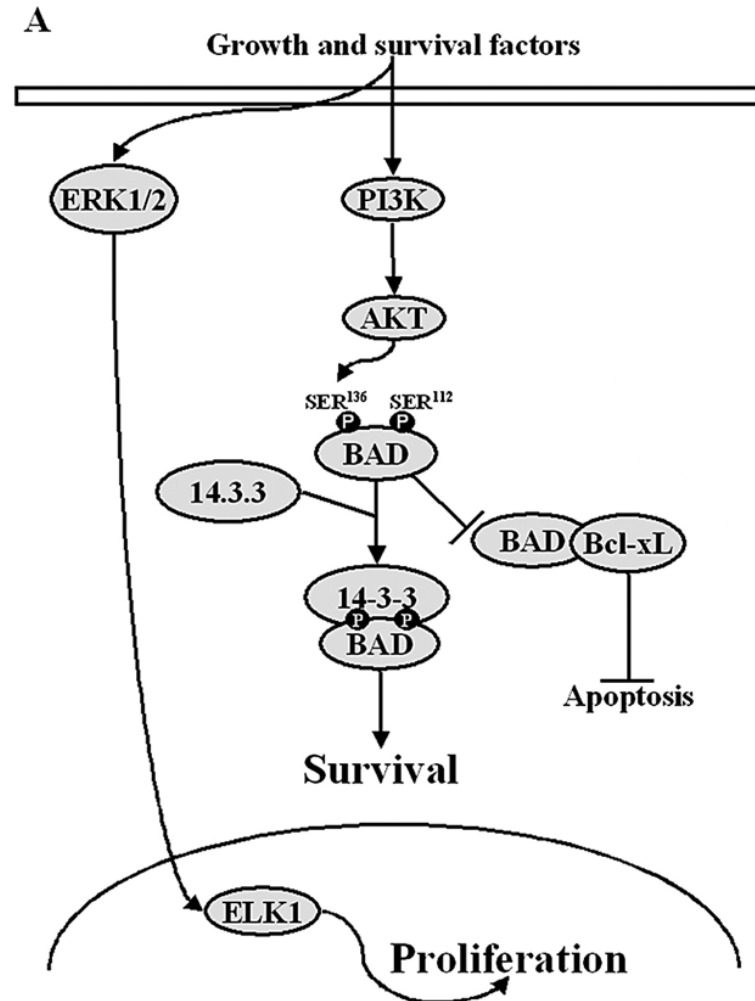
Membrane-bound receptors

- 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 mER α and mER β).



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.
- *Salama SA, et al. (2006) Journal of the Society for Gynecologic Investigation 13: 542-550.*

TGF- β 3

- 2-methoxyestradiol (an estrogen metabolite with anti-tumor properties) inhibits TGF- β 3 profibrotic effects in leiomyoma cells through Smad and non-Smad mediated pathways.

- *Salama SA, Kilic GS,. (2012) Fertil Steril 98: 178-184.*

TGF- β 3

- Furthermore, De Falco and colleagues used tissues obtained from hysterectomy patients and demonstrated that TGF- β 3 and connective tissue growth factor are overexpressed in leiomyoma compared to myometrium.
- *De Falco M, et al. (2006) Journal of the Society for Gynecologic Investigation 13: 297-303.*

TGF- β 3

- Leiomyoma tissue overexpress TGF- β 3 compared to myometrial tissue.

- *Arici A. (2000) Fertil Steril 73: 1006-1011.*

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
- *Eisinger SH et al.(2005) J Minim Invasive Gynecol 12: 227-233.*

Asoprisnil

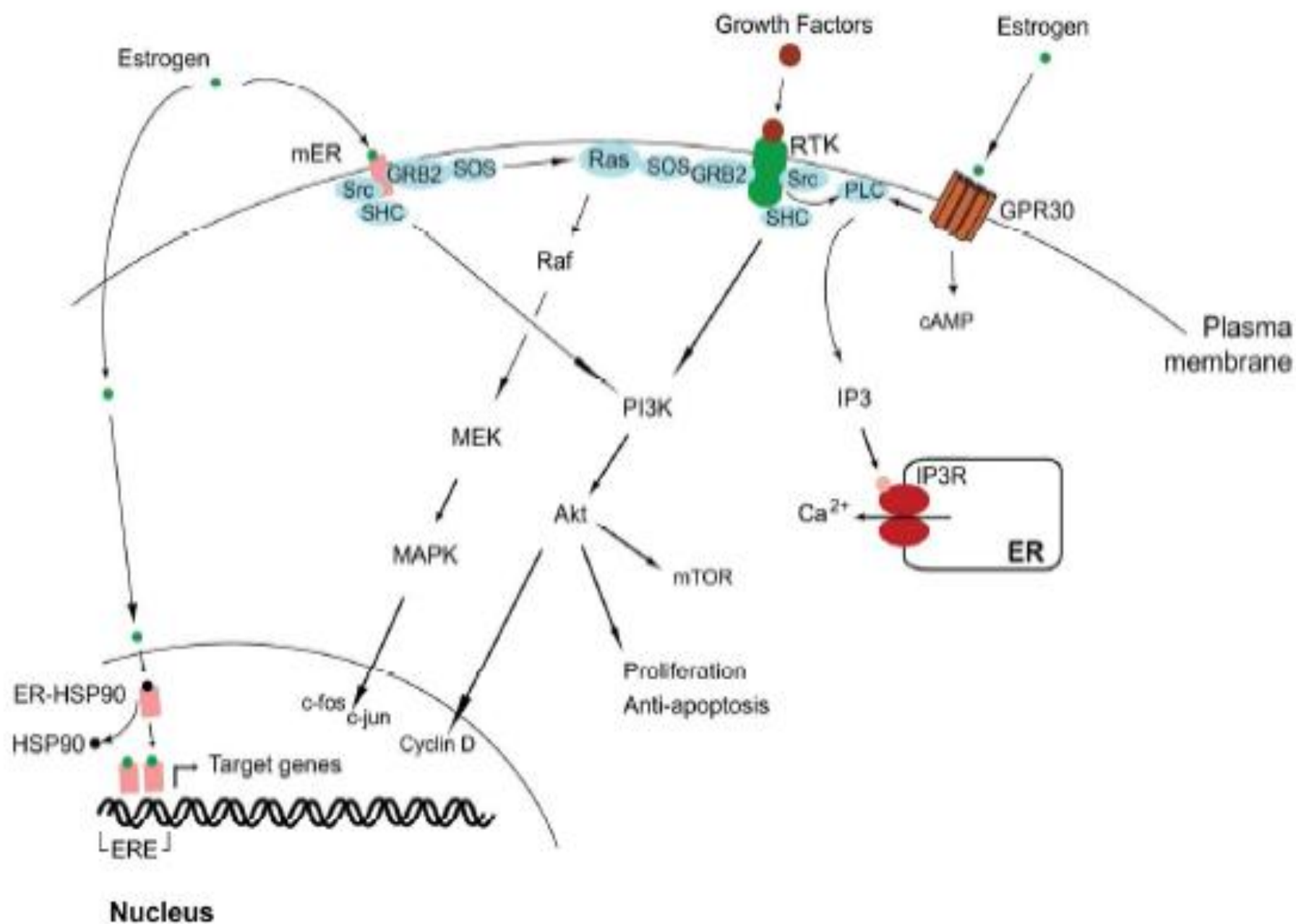
- Induction of apoptotic signaling pathways and inhibition of proliferative signaling pathways. Importantly, these changes were noted in leiomyoma but not myometrial cells.
- *Ohara N, et al. (2007) Reproductive sciences 14: 20-27.*

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
- Sefton EC, et al. (2013) Endocrinology 154: 4046-4057.

Growth Factor

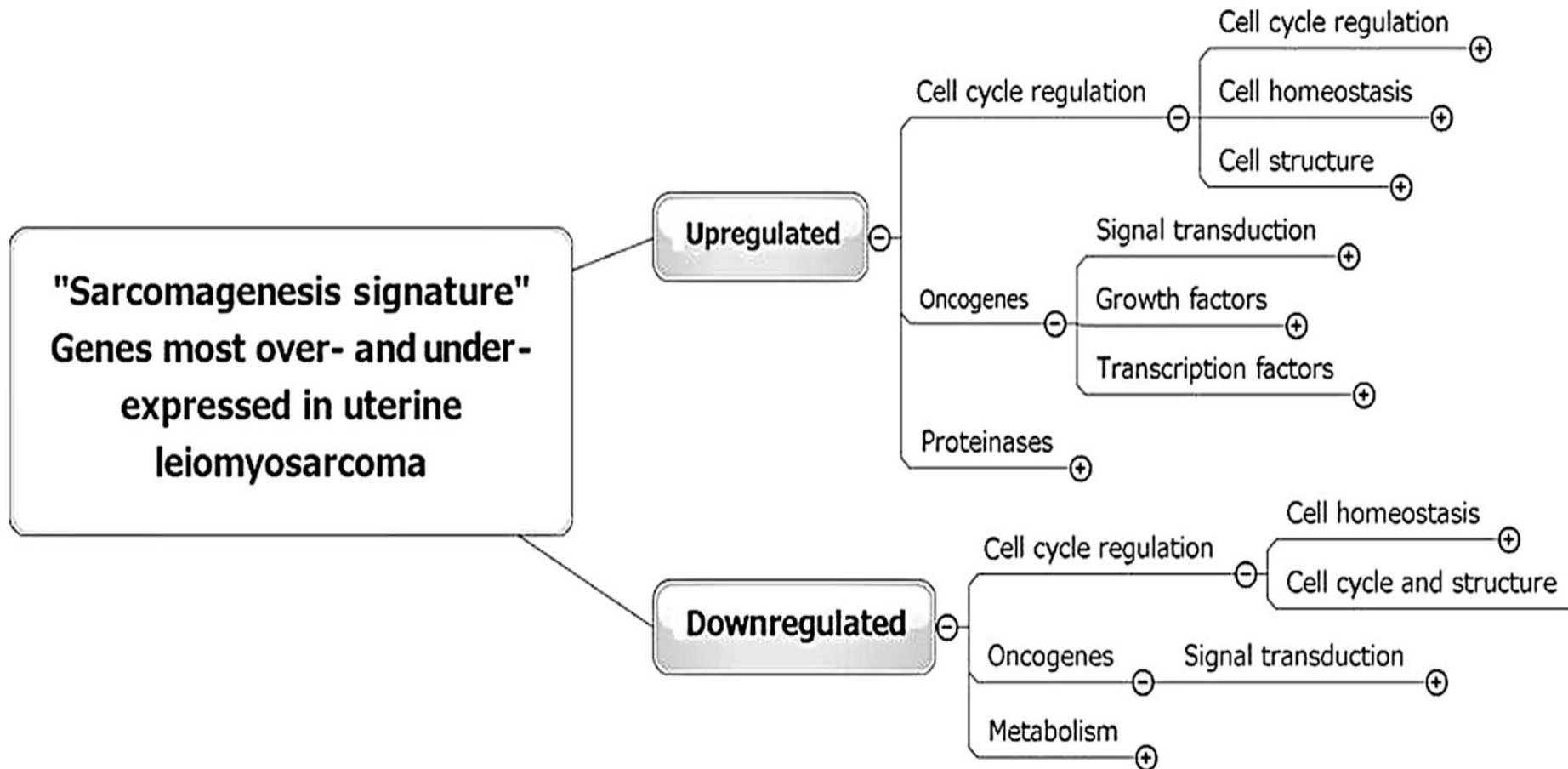
- Growth factor binding to the RTK leads to receptor dimerization and autophosphorylation. This leads to downstream activation of several pathways including Grb2-Sos-Ras-Raf-MEK-ERK and PI3K-PIP3-Akt.



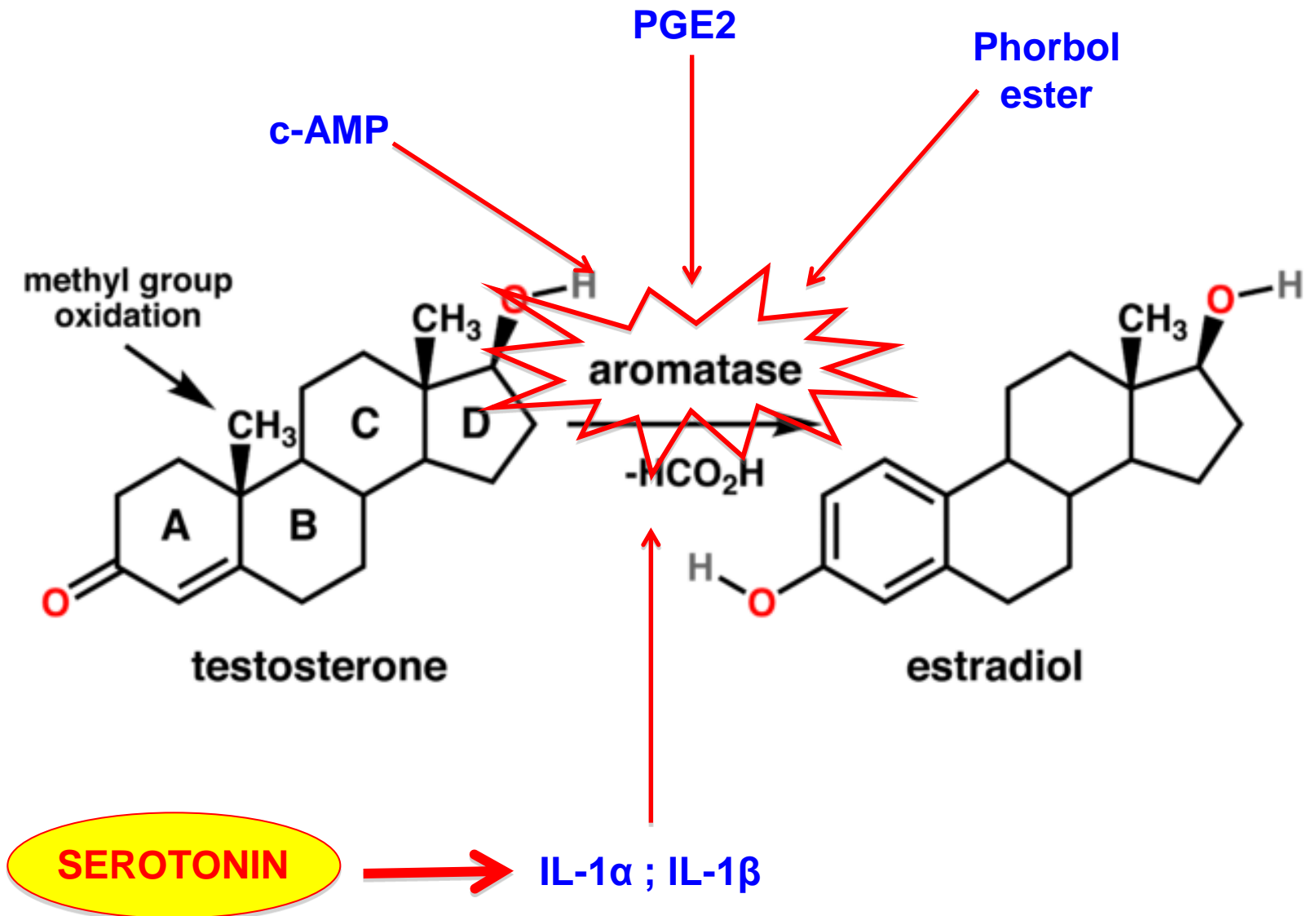
Wnt/beta-catenin

- Estrogen and progesterone-induced proliferation in 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).
- *Ono M, et al. (2013). Proc Natl Acad Sci U S A 110: 17053- 17058.*

Network analysis of key genes involved in leiomyosarcoma development



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.
- *Bulun SE, Simpson ER, Word RA. (1994) J Clin Endocrinol Metab 78: 736-743.*

Aromatase Inhibitors

- Aromatase inhibitors decreased the size of the fibroids

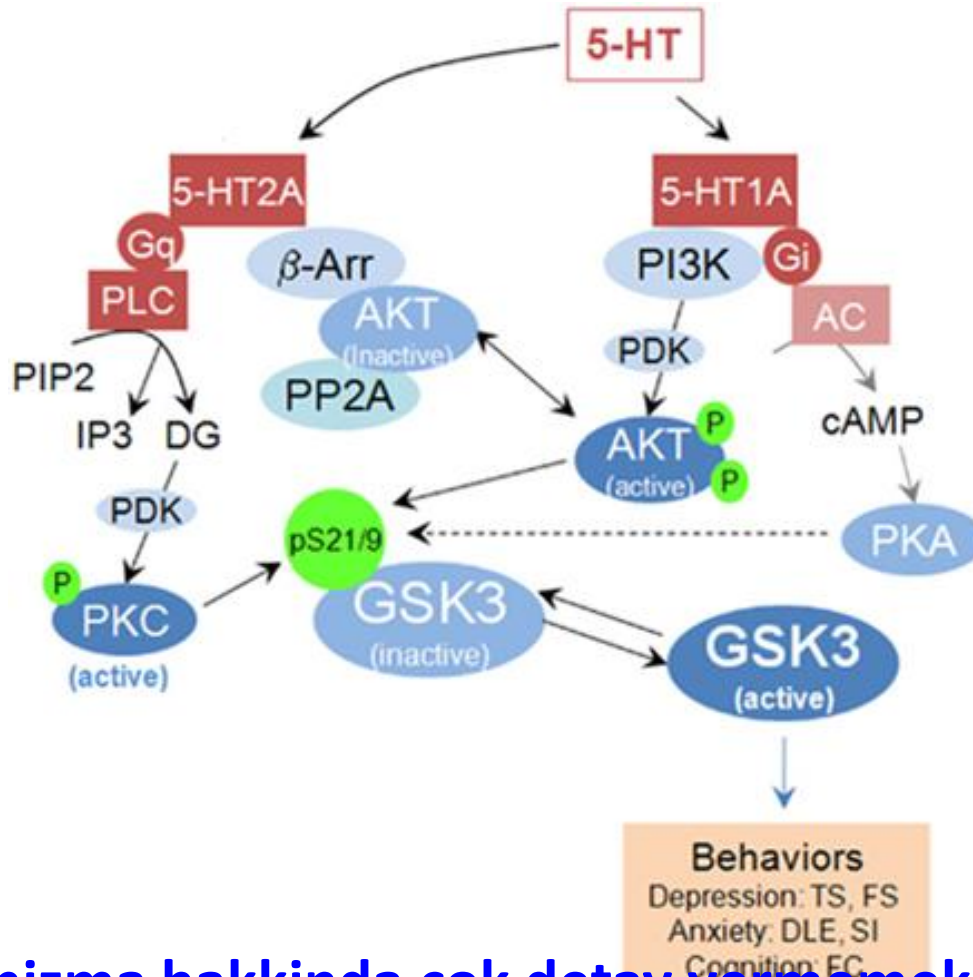


- *Dr. Bilgin Gurates, Kilic GS (2008) Reprod Biomed*

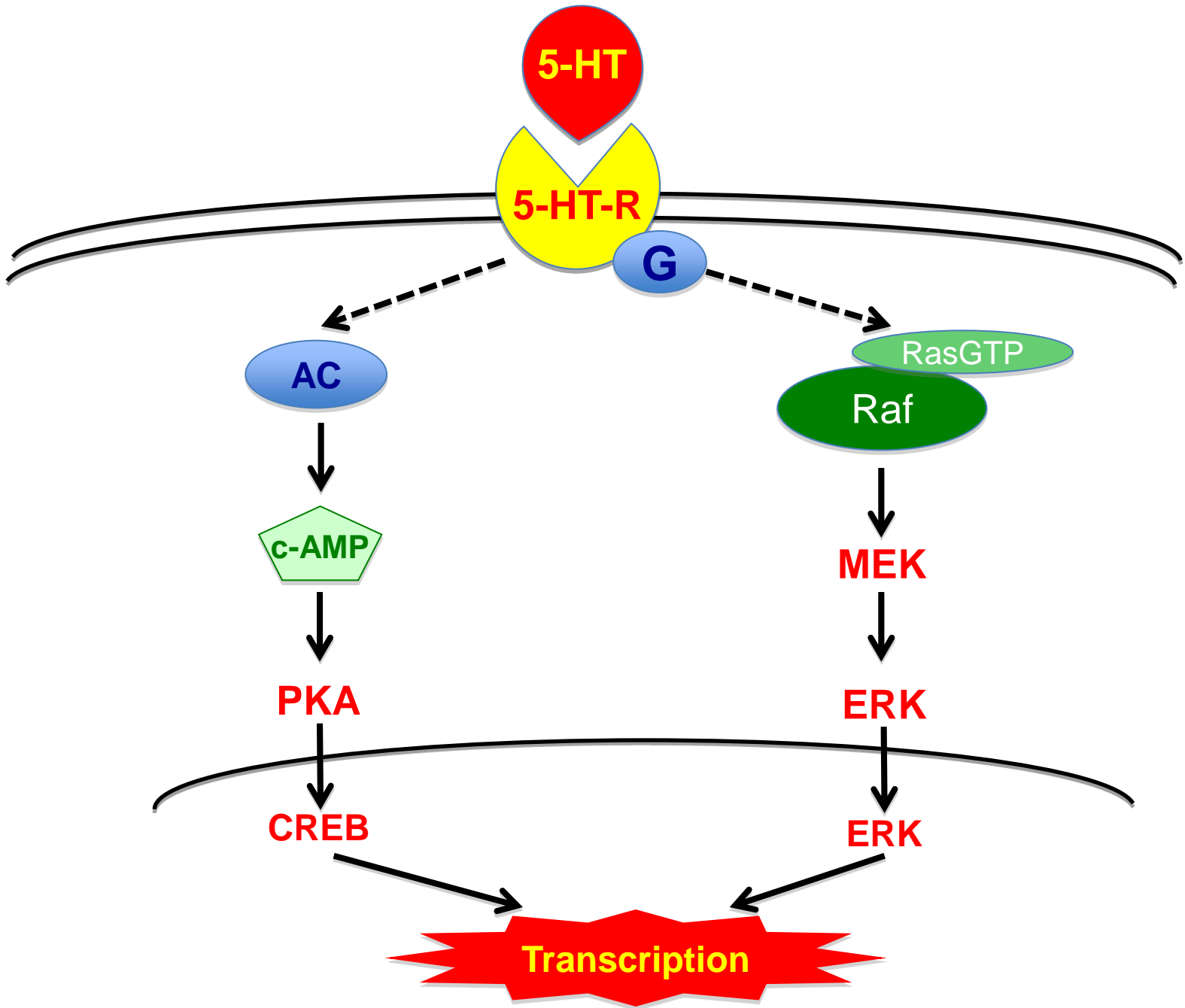
Letrozole

- Three months treatment significantly decreased the size of fibroids without osteroporosis

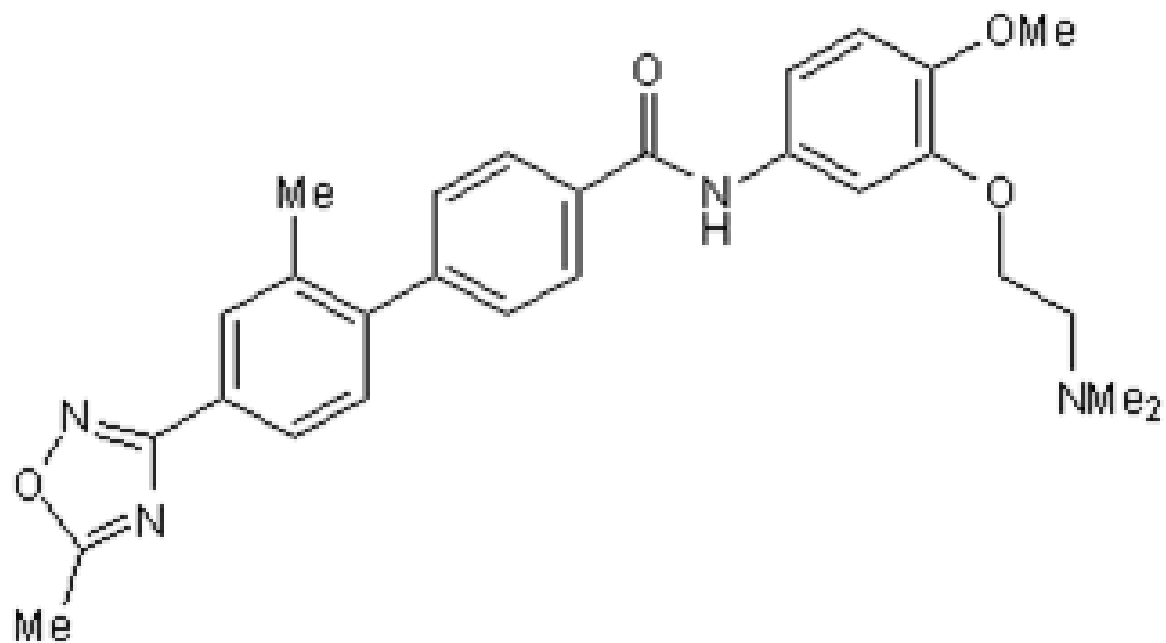
5-HT receptor-mediated signaling pathways



Hocam, mekanizma hakkında çok detay vermemek için isterseniz bu slayti çıkarabilirim!



Chemical structure of SB216641

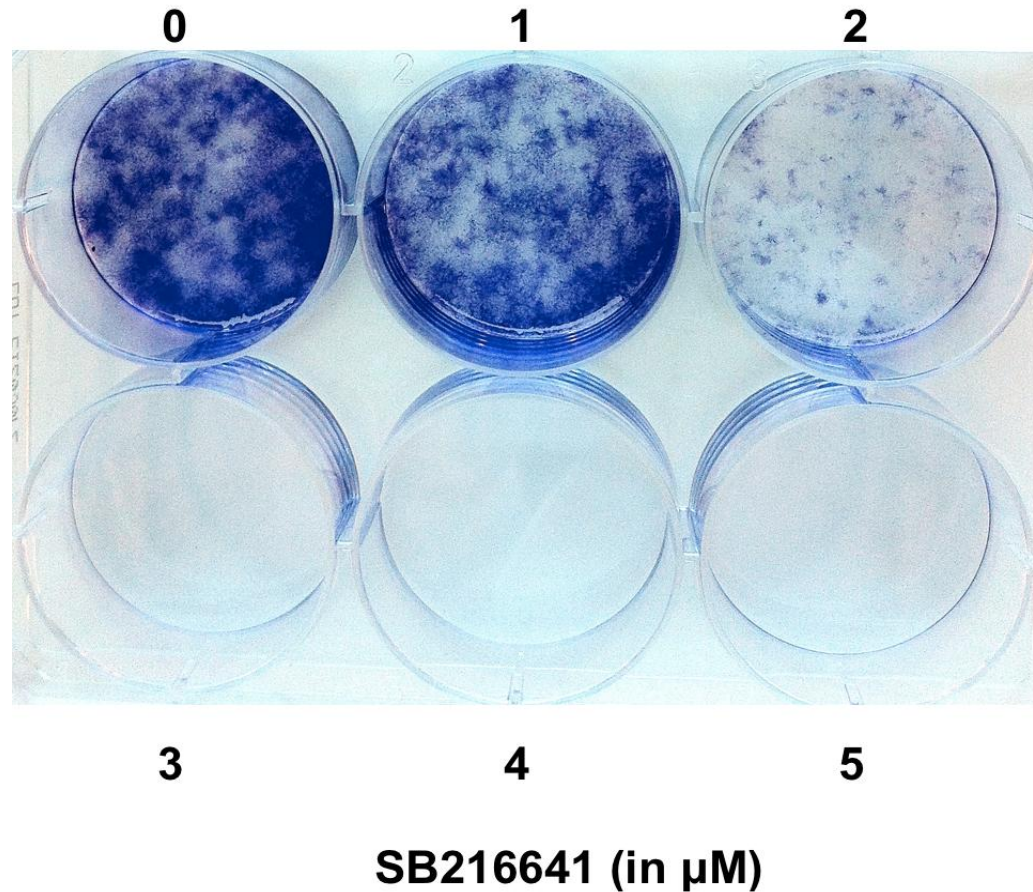


SB216641; A selective 5-HT receptor antagonist.

QUESTION???

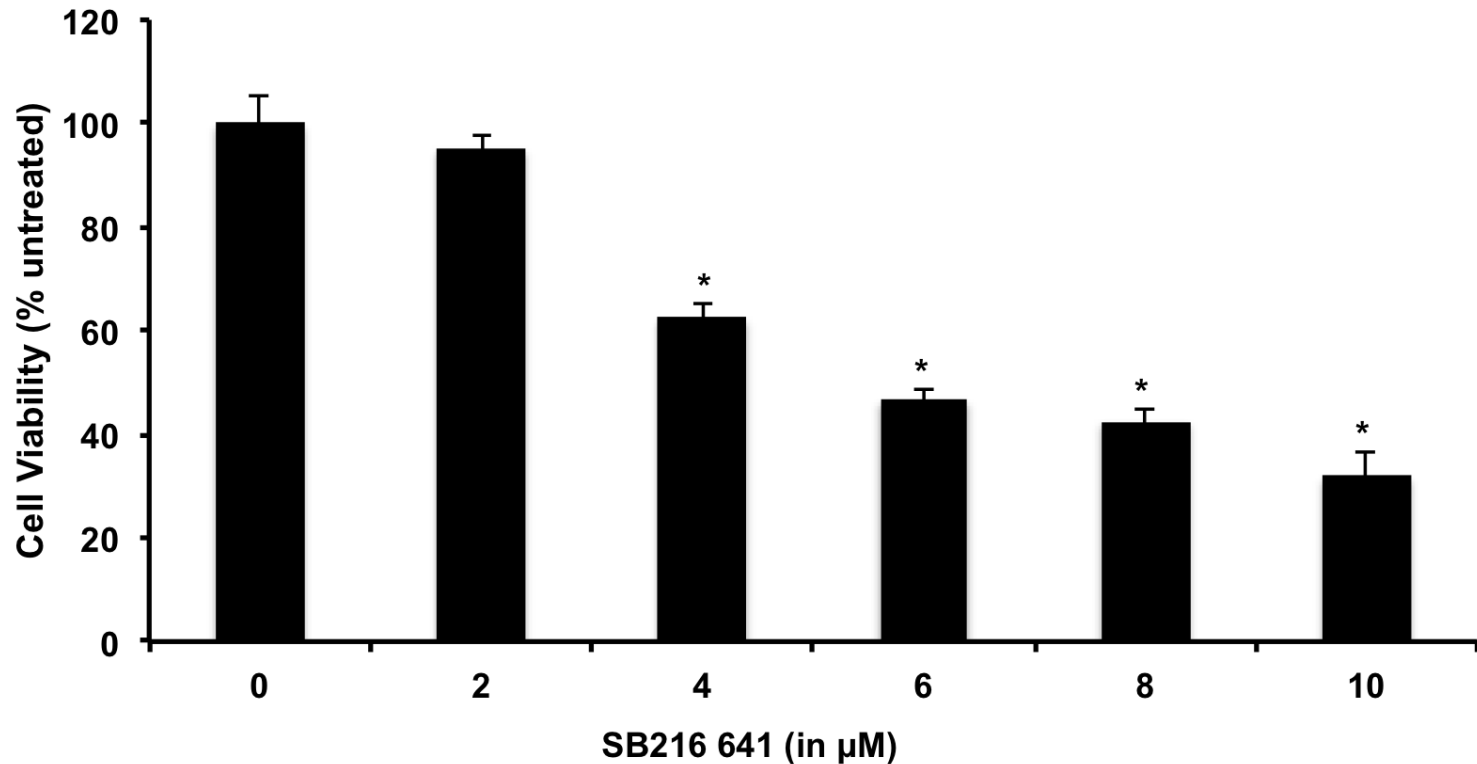
Does SB216641, a selective antagonist of 5-HT receptors, have any therapeutic potential through proliferation and cell death in uterine fibroid cells?

SB216641 decreases cell clonogenicity in a dose dependent manner in huLM cells



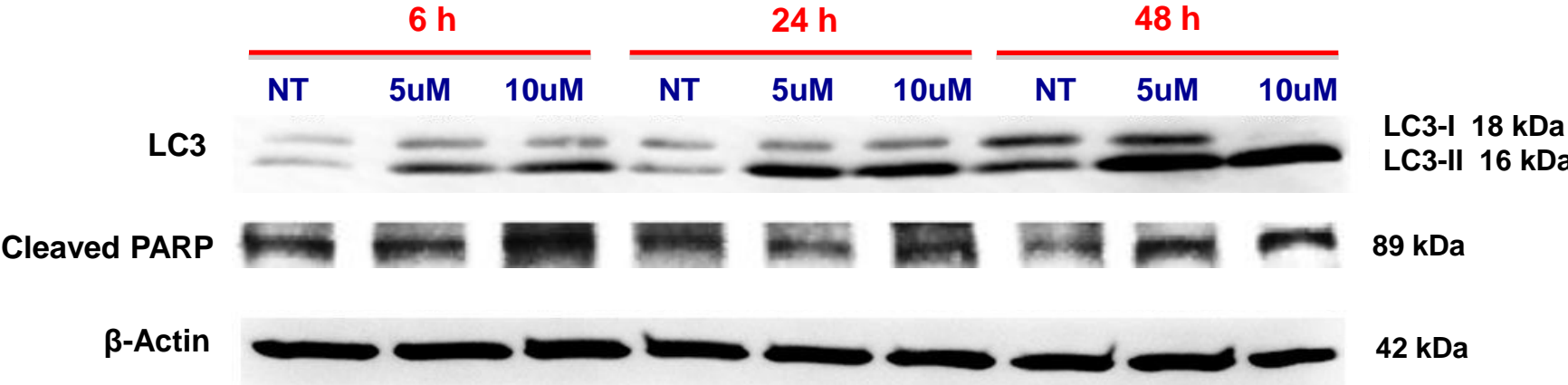
huLM cells were incubated without or with SB216641, 1, 2, 3, 4, 5 μM , for 14 days. The colonies were visualized by crystal violet dye.

SB216641 inhibits the cell viability in a dose dependent manner in huLM cells



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 induces PARP cleavage and autophagosome formation in huLM cells



huLM cells were incubated without or with 5 or 10 μ M SB216641 for 6h, 24h and 48h.

SB216641 induces PARP cleavage and autophagosome formation in huLM cells

