PHARMACOLOGY OF FEMALE SEX HORMONES

TARGETS: estrogen and/or progesterone receptors

STEROID HORMONE BIOSYNTHESIS

HORMONE REPLACEMENT THERAPY (HRT)

- Women’s Health Initiative
  - Estrogen + progesterone: get off HRT!
    - ↑Risk: MI, stroke, breast cancer, thrombosis,
    - ↓Risk: colorectal cancer, osteoporosis
    - No difference: endometrial cancer, overall mortality
  - Estrogen only: no overall benefit (not as dramatic)

- ESTROGEN + PROGESTERONE COMBINATIONS
  - Yasmin, Alesse, Ortho-Evra (transdermal)
  - Estrogen (usually ethinyl estradiol) + progesterone (different types)
  - Conjugated form of estradiol with additional groups added (e.g. SO$_4$) help ↑GI absorption

- PROGESTERONE ONLY
  - Emergency contraceptive (levonorgestrel alone): Plan B, One Step, “morning after pill”
  - MOA: inhibits ovulation, fertilization, implantation

- Mifepristone (RU-486): abortion pill
  - Abortion: terminates early pregnancy within 49 days
  - MOA: competitive antagonist of progesterone receptor

ESTROGEN RECEPTOR SIGNAL TRANSDUCTION

- The estrogen receptor has two isoforms: ER$\alpha$ and ER$\beta$
  - ER$\alpha$: prognostic for breast cancer; turns on growth factors fueling growth of tumor; important drug target & prognostic tool (bad guy)
  - ER$\beta$: located in colon, brain, lung, and breast tissue; present more in normal cells than cancerous; serves as the breaks for breast cancer (good guy)
  - Bad news: ↑ER$\alpha$ + ↓ER$\beta$ (aka ↑growth promoter + ↓breaks)

- There are three estrogen receptor signaling pathways
  - Classical nuclear signaling: estrogen binds to receptor → dimerization → conformational change → binds to estrogen response element (ERE) → gene transcription
    - ERE: recognition site of estrogen receptor made up of a short sequence of DNA within the promoter of a gene that binds to hormone complex and regulates gene transcription
ERE-independent signaling: protein-protein interactions using indirect tethering to transcription factors
- DNA sequence not required, bind to transcription factors instead (not at ERE)
- If more ERα binds → promotes growth
- If more ERβ binds → antagonizes growth

Membrane-initiated signaling: non-genomic signaling
- Estrogen binds to plasma membrane estrogen receptor → activates several signaling molecules → rapid phosphorylation cascades activated
- Needs to piggyback with membrane receptor because it can’t insert itself into membrane

Big picture: estrogen acts on receptors either in the nucleus, plasma membrane, or transcription factors that affect phosphorylation or other signaling pathways

PROGESTERONE RECEPTOR SIGNAL TRANSDUCTION
- Acts the same as the estrogen receptor
- Two isoforms of the progesterone receptor exist: PR-B and PR-A
- Coactivators (histone acetyltransferase activity) & corepressors (histone deacetyltransferase activity)

BREAST CANCER
- Either ER +/- and PR +/- (i.e. whether these receptors are activated or not)
  - ++ = both receptor types activated = active drug target
- ↑Risk of breast cancer: early menses, nulliparity (no kids), late menopause
- ↓Risk of breast cancer: late menses, pregnant <30 y/o, bilateral oophorectomy, early menopause

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)
- “Designer estrogens”
- Functions: treat cancer, chemopreventive
- Tamoxifen (Nolvadex)
  - Mixed estrogen/antiestrogen used in treating and preventing breast cancer
  - Prodrug metabolized by CYP450 to its active metabolite endoxifen
  - If CYP3A4 is affected (e.g. drug interaction, genotype), anticancer effects may be less
  - MOA: blocks estrogen at receptor which ↓downstream signaling
    - When drug binds to receptor, helix is flipped out, which prevents the surface from binding to coactivators while allowing corepressors to bind
- Other SERMS: raloxifene, toremifene
- STAR trial: comparing tamoxifen vs. raloxifene
  - Equally effective in preventing invasive breast cancer
  - Tamoxifen > raloxifene in preventing non-invasive breast cancer
- SERD: selective estrogen receptor downregulator
  - Pure anti-estrogen (not mixed like SERMs) which destroys receptors instead of just blocking them

AROMATASE INHIBITORS
- MOA: inhibits synthesis of estrogen
- Preferred therapy in post-menopausal women
  - Pre-menopausal women produce estrogen (i.e. aromatized) in ovaries whereas in post-menopausal women it is produced in breast tissue, therefore more targeted in post-menopausal women
- Agents: anastrozole (Arimedex), letrozole (Femara), exemastane (Aromasin)
- Due to several key clinical trials, there has been a switch from SERMs to new aromatase inhibitor therapy