DOWNLOAD PDF ESTROGEN RECEPTOR AS A TARGET FOR RATIONAL DRUG DESIGN

Chapter 1 : - NLM Catalog Result

Note: Citations are based on reference standards. However, formatting rules can vary widely between applications and fields of interest or study. The specific requirements or preferences of your reviewing publisher, classroom teacher, institution or organization should be applied.

Estrogen receptor Figure 3: SERM act on the estrogen receptor ER , which is an intracellular , ligand-dependent transcriptional activator and belongs to the nuclear receptor family. This coordination makes the binding of ER to estrogen response elements possible. In agonist-bound receptors, helix 12 is positioned adjacent to helices 3 and 5. Helices 3, 5, and 12 together form a binding surface for an NR box motif contained in coactivators with the canonical sequence LXXLL where L represents leucine or isoleucine and X is any amino acid. In addition, some cofactors bind to ER through the terminals, the DNA-binding site or other binding sites. Thus, one compound can be an ER agonist in a tissue rich in coactivators but an ER antagonist in tissues rich in corepressors. Structural basis for the mechanism of estrogen receptor agonist and antagonist action. When an agonist is bound to a nuclear receptor, the C-terminal alpha helix of the LBD H12; light blue is positioned such that a coactivator protein red can bind to the surface of the LBD. However antagonist ligands in addition have a sidechain extension which sterically displaces H12 to occupy roughly the same position in space as coactivators bind. Hence coactivator binding to the LBD is blocked. Estrogenic compounds span a spectrum of activity ranging from: Pure antagonists antagonistic in all tissues such as fulvestrant. SERMs are known to stimulate estrogenic actions in tissues such as the liver, bone and cardiovascular system but known to block estrogen action where stimulation is not desirable, such as in the breast and the uterus. This makes it easier for the SERMs to interact with estrogen response elements which leads to the activation of estrogen-inducible genes and mediating the estrogen effects. There is growing evidence to support that SERM activity is mainly determined by selective recruitment of corepressors and coactivators to ER target genes in specific types of tissues and cells. Steroid receptor coactivator 3 SRC-3 is phosphorylated by activated kinases that also enhance its coactivator activity, affect cell growth and ultimately contribute to drug resistance. The ratio of ERs in neoplastic and normal breast tissue could be important when considering chemoprevention with SERMs. Together they play an important part in the interaction with other co-regulatory proteins that control gene transcription. The ligand-binding domain of the ER demonstrates how ligands promote and prevent coactivator binding based on the shape of the estrogen or antiestrogen complex. The broad range of ligands that bind to the ER can create a spectrum of ER complexes that are fully estrogenic or antiestrogenic at a specific target site. The binding of ligands to ER leads to the formation of a hydrophobic pocket that regulates cofactors and receptor pharmacology. The correct folding of ligand-binding domain is required for activation of transcription and for ER to interact with a number of coactivators see figure 4. Coactivators play an active role in modifying the activity of a complex. Post-translation modification of coactivators can result in a dynamic model of steroid hormone action by way of multiple kinase pathways initiated by cell surface growth factor receptors. Under the guidance of a multitude of protein remodelers to form a multiprotein coactivator complex that can interact with the phosphorylated ER at a specific gene promoter site, the core coactivator first has to recruit a specific set of cocoactivators. The proteins that the core coactivator assembles as the core coactivated complex have individual enzymatic activities to methylate or acetylate adjacent proteins. The ER substrates or coenzyme A can be polyubiquitinated by multiple cycles of the reaction or, depending on linkage proteins, they can either be activated further or degraded by the 26S proteasome. They have two aromatic rings separated by atoms often a stilbene -type of arrangement. Between the two phenyls of the core, SERMs typically have a 4-substituted phenyl group that, when bound to ER, projects from a position of an estratriene nucleus so that helix 12 moves from the receptor opening and blocks the space where coactivator proteins would normally bind and cause ER agonist activity. There has been a lot of variations in the core portion of SERMs while there has been less flexibility with what is tolerated in the

side chain. First-generation triphenylethylenes[edit] Figure 5: The 3-position H-bonding ability of phenols is a significant requirement for ER binding. Trans-form of clomifene with the triphenylethylene structure in red. The first drug, clomifene 2-[4- 2-chloro-1,2-diphenylethenyl phenoxy]-N,N-diethylethanamine;2-hydroxy-1,2,3-propanetricarboxylate; see figure 6 [34] has a chloro-substituent on the ethylene side chain which produces similar binding affinities as the later discovered drug tamoxifen. Clomifene is a mixture of estrogenic cis-form and antiestrogenic isomers trans-form. However, trans isomer is the most potent stimulator of epithelial cell hypertrophy since clomifene is antagonistic at low doses and agonistic at high doses. In the US, it is also administered for prophylactic chemoprevention in women identified as high risk for breast cancer. Tamoxifen is selectively antiestrogenic in the breast but estrogen-like in bones and endometrial cancer. The major metabolites of tamoxifen are N-desmethyltamoxifen and 4-hydroxytamoxifen. The crystallographic structure of 4-hydroxytamoxifen [37] interacts with the amino acids of the ER within the ligand-binding domain. If its OH group is eliminated or its position is changed the binding affinity is reduced. The hydroxyl group is of particular importance for ER binding of 4-hydroxytamoxifen, and the ethyl side chain of tamoxifen protrudes out of the ligand-binding domain of the ER. The drug can also cause hepatocarcinomas in rats. This is likely due to the ethyl group of the tamoxifen stilbene core that is subject to allylic oxidative activation causing DNA alkylation and strand scission. This problem is later corrected in toremifene. The side chain for tamoxifen cannot neutralize Asp, so the site allosterically influences AF-1 at the proximal end of the ER. This issue is mended with the second-generation drug raloxifene. Chemical structure of toremifene Toremifene toremifene citrate; see figure 8 , chemically designated as 2- p-[Z chloro-1,2-diphenylbutenyl]phenoxy -N,N-dimethylethylamine citrate, is a chlorinated derivative of the nonsteroidal triphenylethylene antiestrogen tamoxifen [5] with a chloro substituent at the ethylene side chain producing similar binding affinities to that of tamoxifen. The presence of the added chlorine atom reduces the stability of cations formed from activated allylic metabolites and thus decreases alkylation potential, and indeed toremifene does not display DNA adduct formation in rodent hepatocytes. Toremifene protects against bone loss in ovariectomized rat models and affects bone resorption markers clinically in a similar fashion to tamoxifen. Toremifene forms its two major metabolites N-desmethyltoremifene and deaminohydroxy-toremifene ospemifene by undergoing N-demethylation and deamination-hydroxylation. N-desmethyltoremifene has similar efficacy as toremifene while 4-hydroxytoremifene has a higher binding affinity to the ER than toremifene. Raloxifene has a benzothiophene group red and is connected with a flexible carbonyl hinge to a phenyl 4-piperidinoethoxy side chain green. Raloxifene [6-hydroxy 4-hydroxyphenyl -benzothiophenyl]-[4-[2- 1-piperidyl ethoxy]phenyl]-methanone; see figure 9 belongs to the second-generation benzothiophene SERM drugs. It has a high affinity for the ER with potent antiestrogenic activity and tissue-specific effects distinct from estradiol. The flexible hinge group, as well as the antiestrogenic phenyl 4-piperidinoethoxy side chain, are important for minimizing uterine effects. When the interactive distance between raloxifene and Asp is increased from 2. When the piperidine ring of raloxifene is replaced by cyclohexane , the ligand loses antiestrogenic properties and becomes a full agonist. It relocates helix 12 away from the ligand-binding pocket thereby preventing coactivators from binding to the SERM-ER complex. Chemical structure of nafoxidine with the dihydronapthalene group in red. Third-generation compounds display either no uterine stimulation, improved potency, no significant increases in hot flushes or even a combination of these positive attributes. Nafoxidine has all three phenyls constrained in a coplanar arrangement like tamoxifen. But with hydrogenation, the double bond of nafoxidene were reduced, and both phenyls are cis-oriented. The amine-bearing side chain can then adopt an axial conformation and locate this group orthogonally to the plane of the core, like ralofoxifene and other less uterotropic SERMs. Chemical structure of lasofoxifene shows cis-oriented phenyls. Lasofoxifene is among the most potent SERMs reported in protection against bone loss and cholesterol reduction. The excellent oral potency of lasofoxifene has been attributed to reduced intestinal glucuronidation of the phenol. The structural requirement is a non-planar topology with the steric bulk close to the plane of a fused bicyclic aromatic system. Lasofoxifenes

large flexible side chain terminates in a pyrrolidine head group and threads its way out toward the surface of the protein, where it interferes directly with the positioning of the AF-2 helix. A salt bridge forms between lasofoxifene and Asp The charge neutralization in this region ER may explain some antiestrogenic effects exerted by lasofoxifene. Bazedoxifene includes an indole system red which is connected to an amine through a benzyloxyethyl chain green. The indole system has served as a core unit in SERMs, and when an amine is attached to the indole with a benzyloxyethyl, the resultant compounds were shown to have no preclinical uterine activity while sparing rat bone with full efficacy at low doses. Bazedoxifene 1H-indool,1-[[4-[2 hexahydro-1H-azepinyl ethoxy]methyl]2- hydroxyphenlyl methyl; see figure 10] acetic acid is one of those compounds. The core binding domain consists of a 2-phenylmethyl indole and a hexamethylenamine ring at the side chain affecter region. It is metabolized by glucuronidation, with the absolute bioavailability of 6. It has agonistic effects on bone and lipid metabolism but not on breast and uterine endometrium. Chemical structure of ospemifene. Ethoxy side chain ends with a hydroxy group red instead of a dimethylamino group as with first-generation SERMs. Ospemifene Z 4- 4-chloro-1,2-diphenyl-butenyl phenoxy ethanol; see figure 13 is a triphenylethylene and a known metabolite of toremifene. Ospemifene does not have 2- dimethylamino ethoxy group as tamoxifen. Structureâ€”activity relationship studies shoved that by removing that group of tamoxifen agonistic activity in the uterus was significantly reduced, but not in bone and cardiovascular system. Preclinical and clinical data show that ospemifene is well tolerated with no major side effects. Benefits that ospemifene may have over other SERMs is its neutral effect on hot flushes and ER-agonist effect on the vagina, improving the symptoms of vaginal dryness. In addition, the structure of the ligand must be rigid. Repulsive interactions may otherwise lead to conformational change of the ligand and, therefore, creating alternative binding modes. The receptor recognition of 4-hydroxytamoxifen appears to be controlled by two structural features of 4-hydroxytamoxifen, the phenolic A ring, and the bulky side chain. The bulky side chain, protruding from the binding cavity, displaces helix 12 from ligand-binding pocket to cover part of the coactivator binding pocket. The ERhydroxytamoxifen complex formation recruits corepressors proteins. This leads to decreased DNA synthesis and inhibition of estrogen activity. Just like in 4-hydroxytamoxifen, the bulky side chain of raloxifene displaces helix A timeline of when SERMs came on the market is seen in figure 1. Clomifene and tamoxifen prevented conception in rats but did the opposite in humans. Clomifene successfully induced ovulation in subfertile women and on February 1, , it was approved in the US for the treatment of ovulatory dysfunction in women who were trying to conceive. Timeline of when SERMs came on the market. It was another ten years before tamoxifen was approved in December , not as a contraceptive but as a hormonal treatment to treat and prevent breast cancer. Combined therapy with conjugated estrogens and the SERM bazedoxifene , was approved on October 3, , for the treatment of vasomotor symptoms linked with menopause. Bazedoxifene is also used in the prevention of postmenopausal osteoporosis.

DOWNLOAD PDF ESTROGEN RECEPTOR AS A TARGET FOR RATIONAL DRUG DESIGN

Chapter 2 : Chemist has designs on drug-resistant breast cancer

This text is concerned with the oestrogen receptor as a biochemical target for the design of new agents useful for the therapy and diagnosis of oestrogen-related diseases such as carcinomas of the.

Blocking estrogen production aromatse inhibitors and the binding to the estrogen receptor tamoxifen are mainstays of treatment for patients with ER estrogen receptor and PR progesterone receptor positive breast cancer. However, patients relapse subsequent to treatment with these agents. The ER acts as a nuclear transcription factor, which potentiates the transcription of genes driving proliferation and apoptosis inhibition see diagram from Clinical Cancer Research. Cross-talk between signal transduction pathways and ER signaling in endocrine-resistant breast cancer, with opportunities for targeted intervention. Modulating these pathways by various signal transduction inhibitors may overcome the resistance to endocrine therapy. SERDs are designed to not only block estradiol action at the estrogen receptor, but eliminate the ER by changing its conformation such that the cell targets the ER for destruction. This would provide a much more efficient and complete blockade of the ER. ARN is in early clinical studies Phase 1 , which is why this sort of deal stands-out. Normally, a big company like Genentech would license the product at this stage, but here, they bought the whole company. Because, Seragon is a company that has a very successful history of developing first in class products for hormone-driven diseases. This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. CYP17 catalyzes two sequential reactions: DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals. The AR is a nuclear receptor transcription factor; upon binding with DHT dihydroxytestoerone , it translocates to the nucleus and induces the transcription of genes that promote growth and survival like the ER. See diagram in BOLO. First, in castration-resistant prostate cancer, the cancer itself begins to produce testosterone autocrine growth and the testosterone receptors become much more sensitive to even low levels of androgen. Further, even low levels of testosterone that result from adrenal gland production can drive the tumor. So, blocking the biosynthesis of testosterone, as opposed to the signals for its production or its receptor binding is a much more efficient and ubiquitous way to achieve androgen deprivation therapy see diagram from Nature Reviews. Methods of achieving androgen deprivation for prostate cancer.

Chapter 3 : Selective estrogen receptor modulator - Wikipedia

*The Estrogen Receptor As Target for Rational Drug Design (Molecular Biology Intelligence Unit) [Erwin, Ph.D. Von Angerer] on calendrierdelascience.com *FREE* shipping on qualifying offers.*

Chapter 4 : Hormone Receptors | Cancer Biology

This entry was posted in Angiogenesis, Cell Cycle, Growth Receptors, Hormone Receptors, Mutations, Off-Target Effects, Oncogenes, Rational Drug Design, Receptor Tyrosine Kinase Inhibitors, Signal Transduction, Uncategorized and tagged acneiform rash, Erivedge, Hedgehog, Targeted Cancer Therapies, vismodegib, Xtandi on August 1, by Joseph.