PXR et al.

TLX – Tailless orphan receptor

• Tlx is a member of the *tailless* class of orphan nuclear receptors, a highly conserved family in both vertebrates and invertebrates.

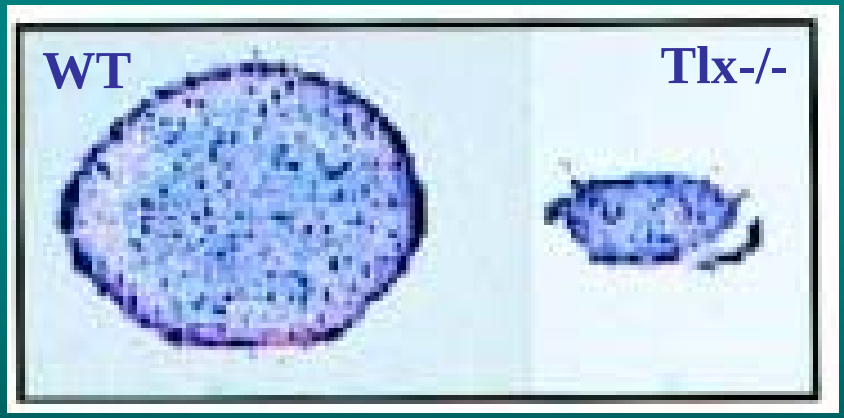
• The evolutionary conservation of the pattern of Tlx expression in the embryonic forebrain, midbrain, and optic vesicle in vertebrates suggested that Tlx may participate in the formation of central nervous system-derived structures.

• Orphan receptor that binds DNA as a monomer.

• In mice it is required to brain differentiation.

• Involved in the regulation of retinal development and essential for vision.

• $TLX^{-/-}$ mice show:



Section through optic nerves

* central nervous system cortical defects
* progressive retinal and optic nerve degradation with associated blindness.

TLX – Tailless orphan receptor

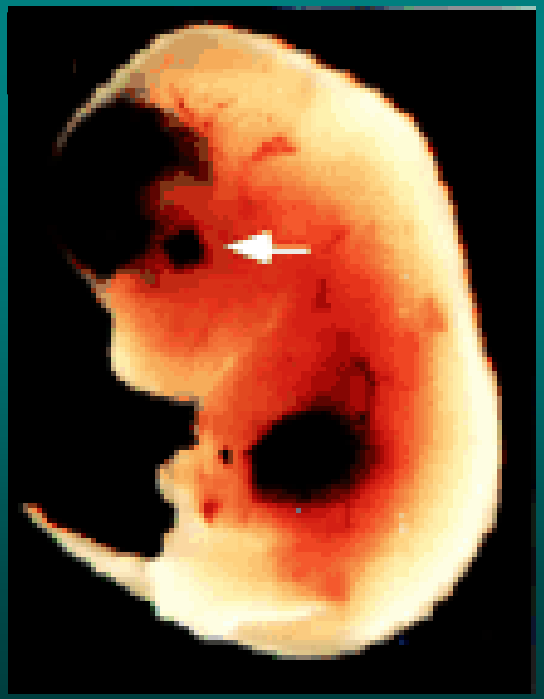
- TLX was initially identified as an orphan nuclear receptor expressed in vertebrate forebrains and is highly expressed in the adult brain.

- The brains of TLX-null mice have been reported to have no obvious defects during embryogenesis; however, mature mice suffer from retinopathies, reduced copulation and progressively violent behaviour.

- The finding of neurogenesis in the adult brain led to the discovery of adult neural stem cells

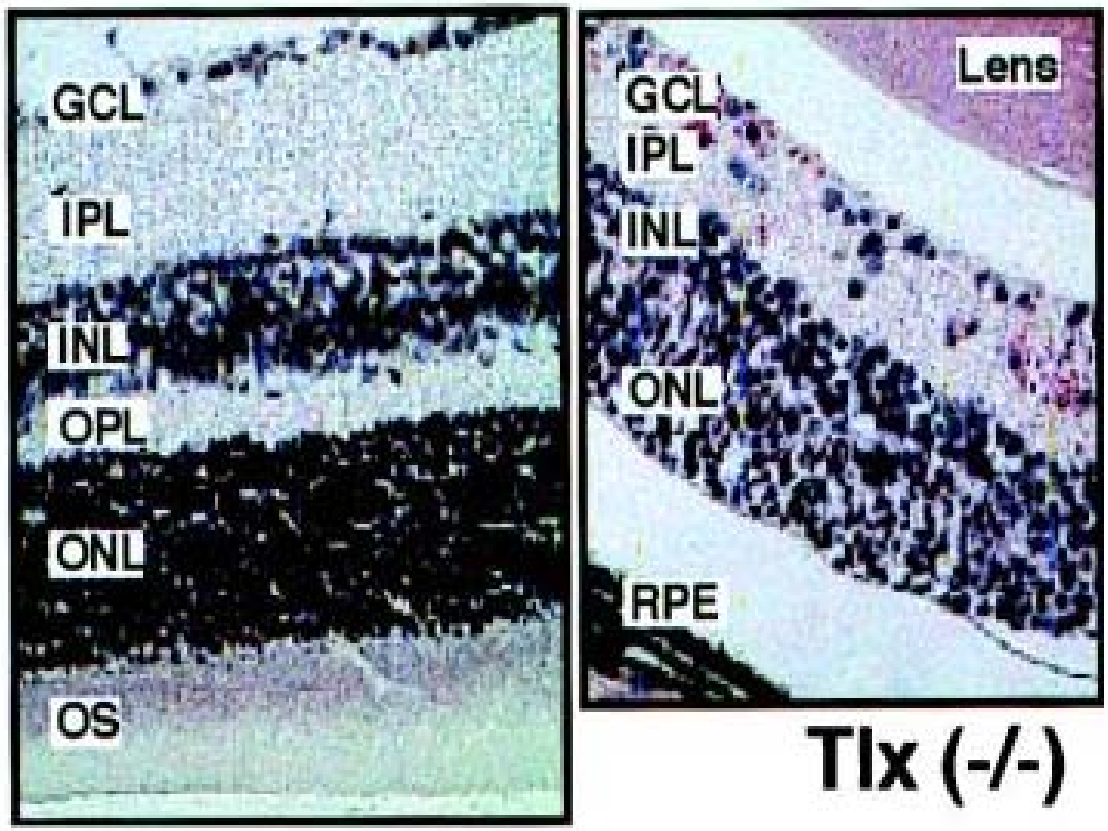
- TLX maintains adult neural stem cells in an undifferentiated, proliferative state. TLX-expressing cells from adult brains can proliferate, self-renew and differentiate into all neural cell types *in vitro*. By contrast, TLX-null cells from adult mutant brains fail to proliferate.

- Thus, TLX plays a role in adult neurogenesis.



TLX

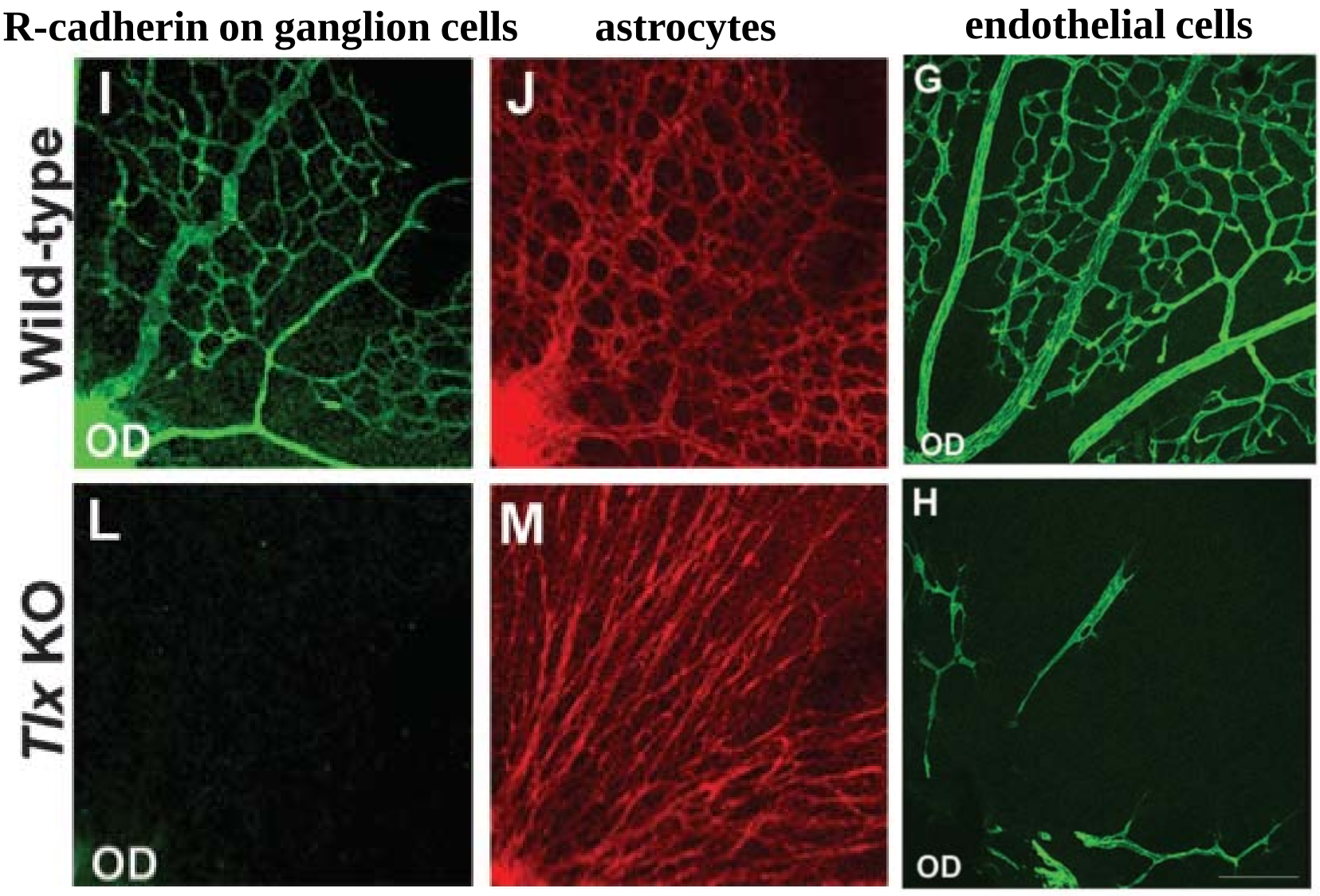
- **In neural precursors the target gene for TLX is Pax2, a protein involved in retinal development.**
- **Tlx is a key component of retinal development and vision acting as an upstream regulator of the Pax2 signaling cascade.**



Histological sections through the eye of a WT and Tlx−/− mouse showing disorganization of the ganglion cell layer (GCL) and the inner (INL) and outer nuclear layers (ONL) as well as absence of outer plexiform and outer segment layers.

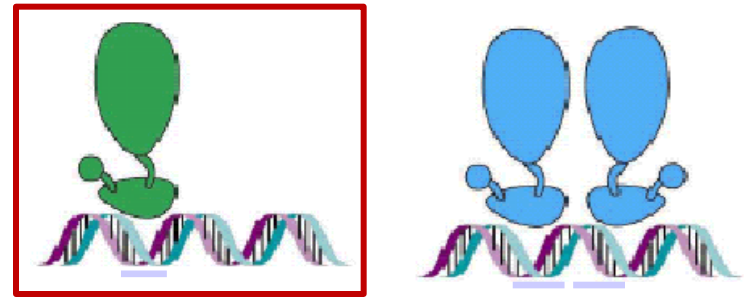
IPL, inner plexiform layer;
OPL, outer plexiform layer;
OS, outer segments;
RPE, retinal pigmented epithelium.

Morphogenetic defects in network formation of *Tlx* KO mice



ROR – Retinoic Acid Receptor Related Orphan Receptor

- Three ROR isotypes (α, β, γ) have been described, all acting as monomers (sometimes as homodimers):
  * RORα: development of cerebellum and lymph nodes, lipid metabolism, immune response, maintenance of bone, muscle differentiation
  * RORβ: highly expressed in the brain and retina
  * RORγ: lymph node development, survival of Th17 cells



- ATRA is a ligand for RORβ and RORγ (not for RORα)

- RORα was initially described as an orphan receptor and has long been considered a constitutive activator of transcription in the absence of exogenous ligand. Crystallization and binding assays revealed that there are ligands:
  * cholesterol
  * 7-dehydrocholesterol (provitamin D3)

- Depletion of cholesterol in cells using the statin dramatically decreases the activity of RORα, suggesting that changes in intracellular cholesterol level are capable of modulating the transcriptional activity of ROR.

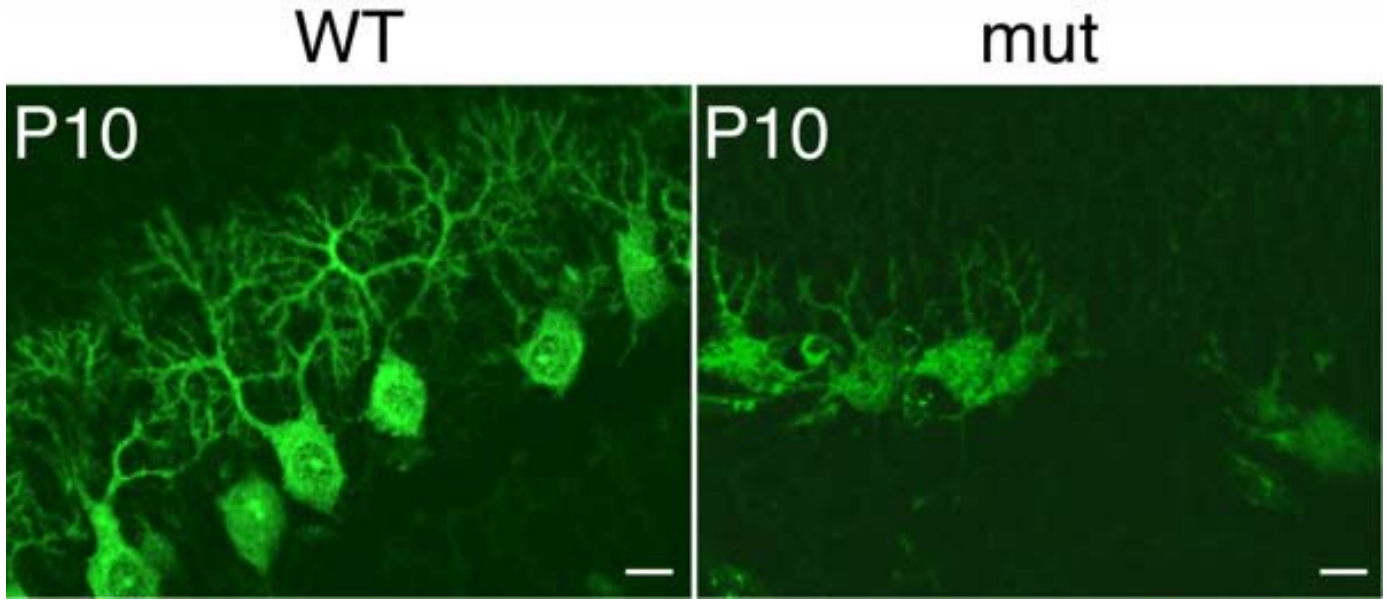
- RORα can be studied using sg/sg mice, carrying a spontaneous mutation the RORα. They have significant changes in age-realted phenotypes.

RORα – cerebellar degeneration

- In the cerebellum, the loss of function of the ROR protein causes a cell-autonomous developmental defect of the Purkinje cells (~80% is lost adult mice).

- Purkinje cells seem to be generated in a normal number at the embryonic stage, but undergo cell death most likely between postnatal ages of 0 and 5 days.

- The molecular mechanisms underlying the cerebellar phenotype are still not understood, but it appears that ROR plays a neuroprotective role during development and ageing.



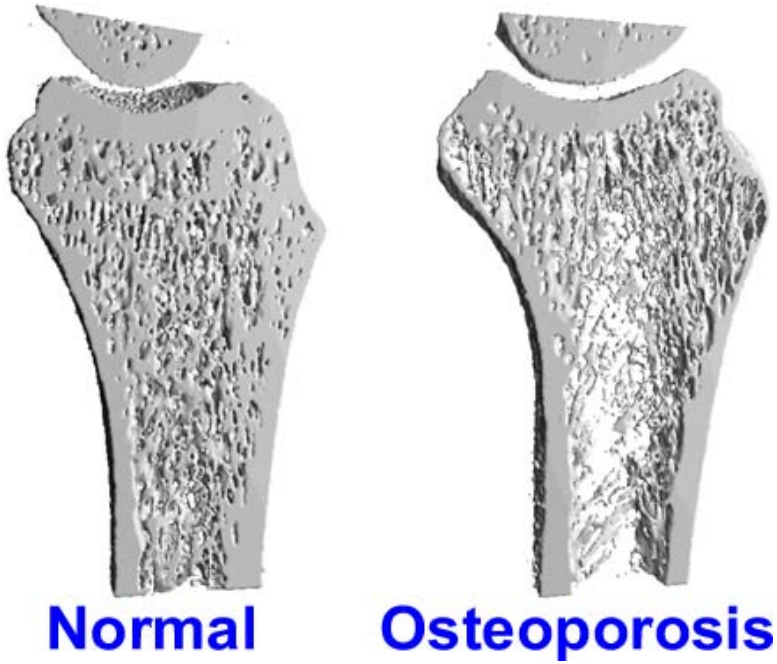
http://www.its.caltech.edu/~chanlab/Research%20images/Purkinje.jpg

RORα – osteoporosis

- Susceptibility to osteoporosis has been revealed in sg/sg mutant, and RORα has been implicated in bone formation and maintenance.

- Bones of sg/sg mice are thin, long, and osteopenic.

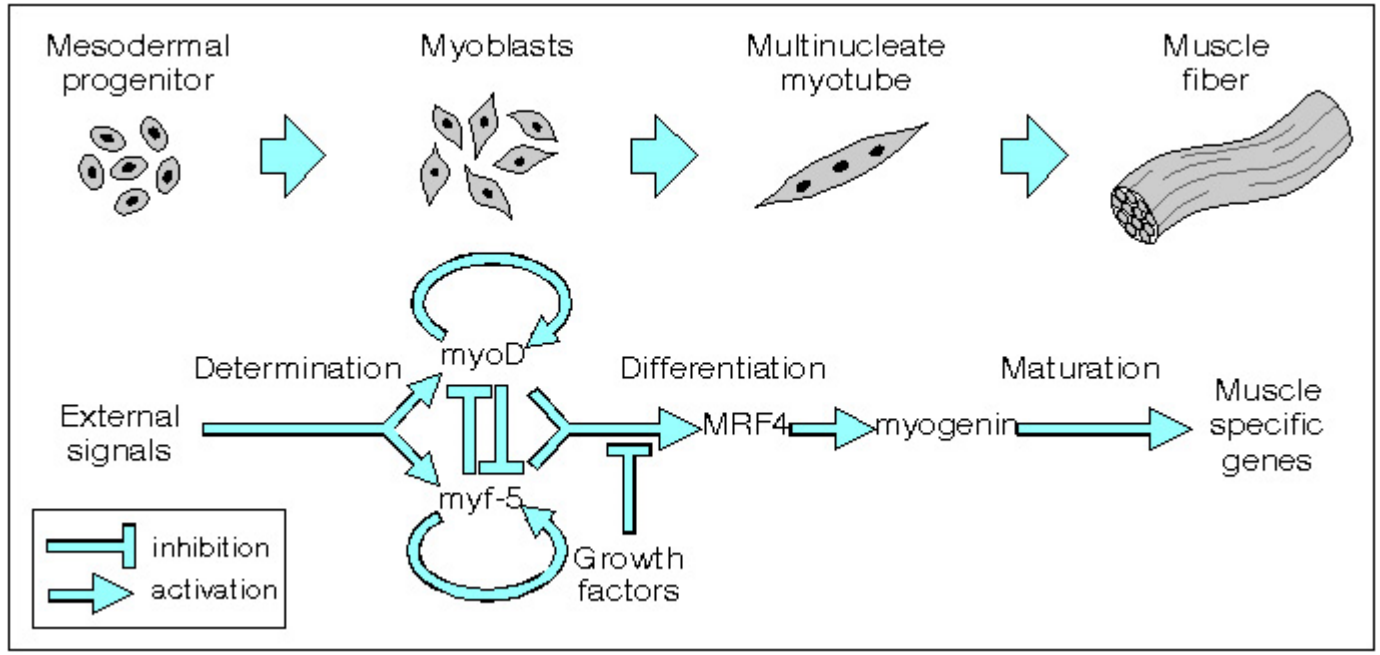
- ROR expression in mesenchymal stem cells derived from bone marrow is increased during the osteogenic differentiation. A direct control by ROR on mouse bone sialoglycoprotein and osteocalcin gene promoter has been characterized and may account in part for the mechanism of action.



RORα – skeletal muscle

- RORα is expressed in skeletal muscle and in proliferating myoblasts.

- RORα has a positive influence on muscular development via the upregulation of MyoD transcription factor, the major regulator of myogenesis. MyoD activates muscle specific gene transcription and promotes cell-cycle exit after the induction of differentiation. Thus, RORα positively regulates myogenesis.



RORα in the vascular system

- In the vascular system RORα is involved in:
  * differentiation of vascular smooth muscle cells (VSMC),
  * control of the vascular tone of small arteries,
  * ischemia-induced angiogenesis,
  * lipid metabolism,
  * inflammation.

- **RORα** mRNA is expressed in VSMC and endothelial cells (EC), and can be **upregulated after treatment with interleukin IL-1β, TNF, and LPS**. Its expression is, however, significantly decreased in atherosclerotic plaques.

- **RORα promotes in the differentiation of VSMC** of small arteries: in sg/sg mice, the expression of VSMC differentiation markers (calponin and h-caldesmon) is reduced.

- **RORα is involved in the regulation of vascular tone** of small resistance arteries: arteries of sg/sg mice display lower mean blood pressure. The vascular reactivity of arteries in response to vasoconstrictors and to endothelium-dependent or -independent vasodilators is also impaired.

- VSMC from sg/sg mice display a reduced expression of the contractile protein SM-myosin, which might account for the decrease in contractile function. Thus, **RORα seems to be essential in the differentiation and contractile function of SMC.**

ROR and angiogenesis

- The role of ROR in angiogenesis has been assessed by studying sg/sg mice with induced hindlimb ischemia.

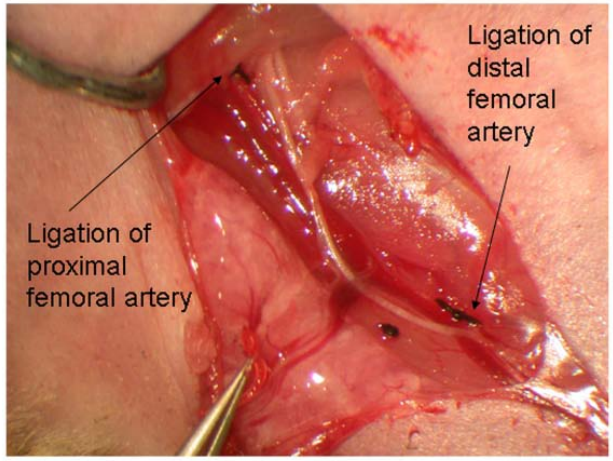
- Femoral artery ligation induces a rapid and transient increase in ROR mRNA in ischemic tissue. In sg/sg mice, angiogenesis is markedly enhanced after ischemia:

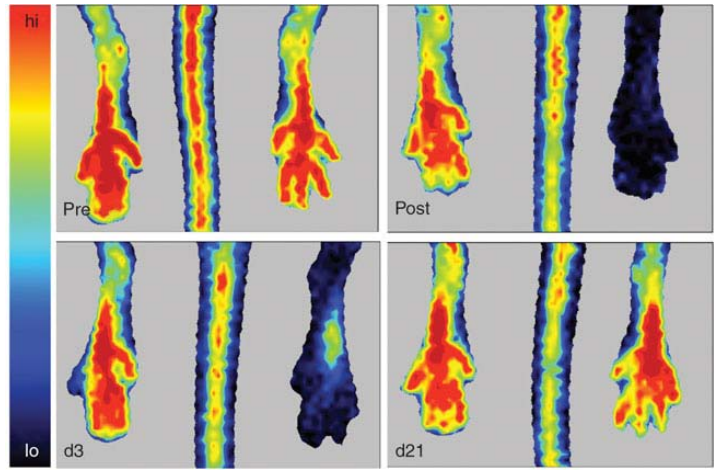
*** capillary density is increased**

*** leg perfusion is improved.**

- Endothelial nitric oxide synthase (eNOS) protein expression is increased in sg/sg mice, whereas the levels of antiangiogenic cytokine IL-12 are significantly reduced.

Thus, RORα is a potent negative regulator of ischemia-induced angiogenesis.

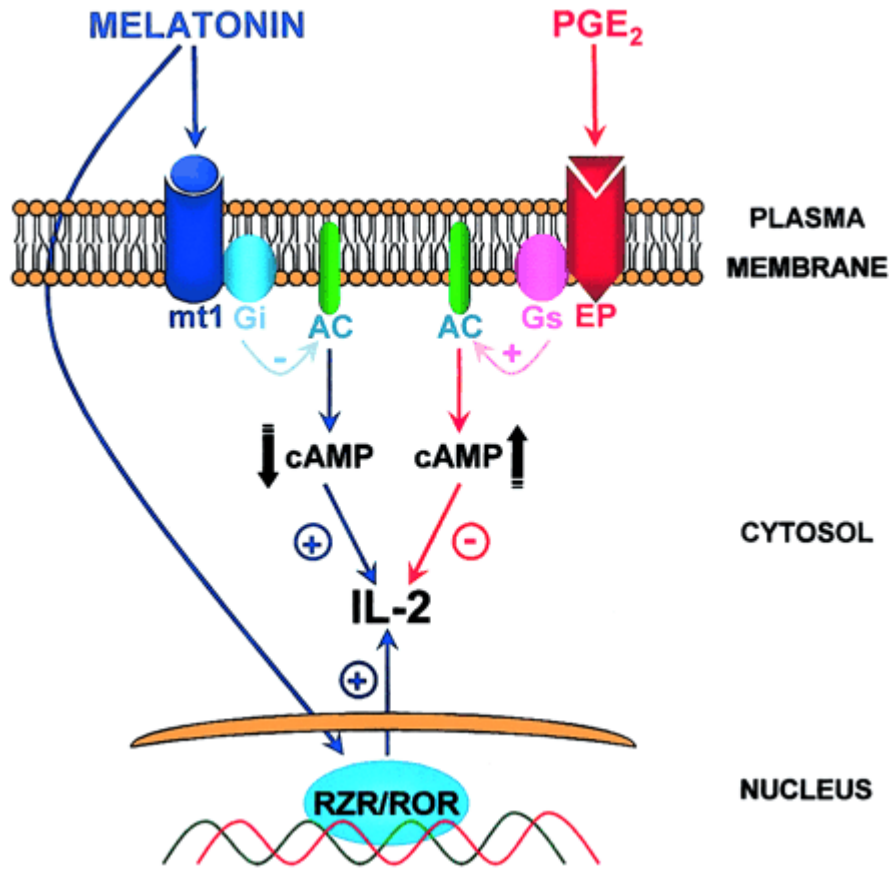




RORα (RZR)

- **RORα is the receptor for the pineal gland hormone melatonin. It binds as a monomer to DNA, and the human 5-lipoxygenase gene has been identified as the ROR/melatonin-responding gene.**

- **COUP-TF is a nuclear receptor which binds as a homodimer to DNA and can bind with high affinity to some of the monomeric ROR response elements in response to melatonin:**
  - *** bone sialoprotein,**
  - *** Purkinje cell protein 2,**
  - *** p21**

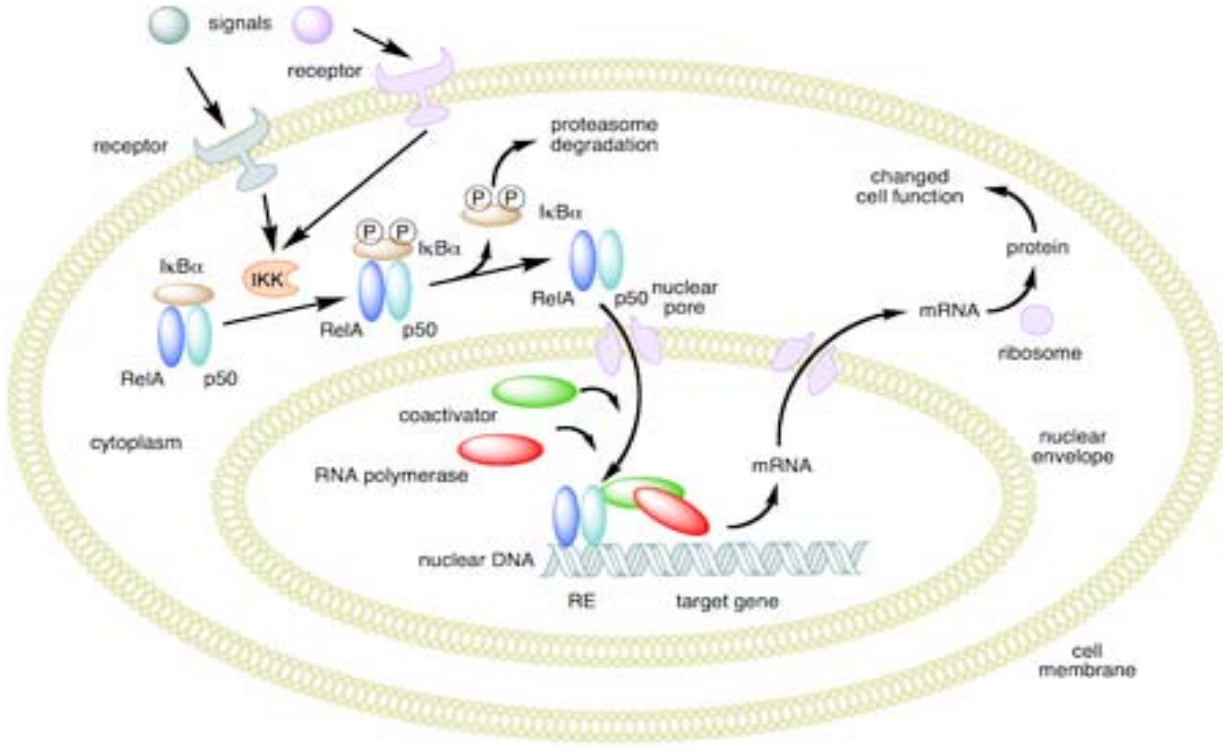


RORα and inflammation

- **Homozygous sg/sg mutants have a delayed thymic development and a defect in terminating T-cell responses.**

- **Peripheral macrophages of sg/sg mice produce abnormally high amount of proinflammatory cytokines IL-1β, IL-6, and TNF (macrophage hyperexcitability)**

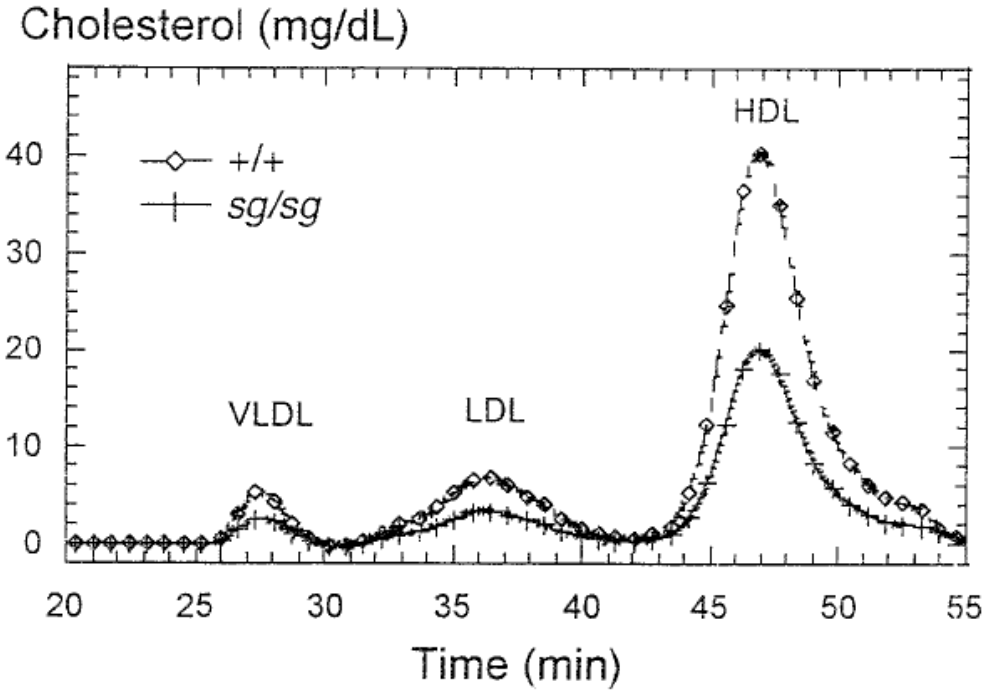
- **Antiinflammatory activities of ROR result from the inhibition of NFkB signaling pathway by inducing IkB gene expression.**

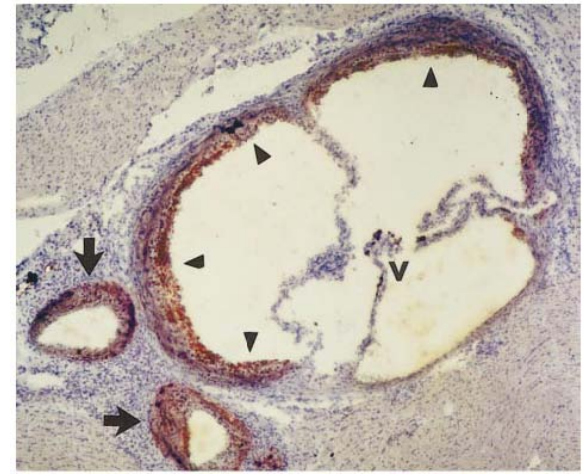


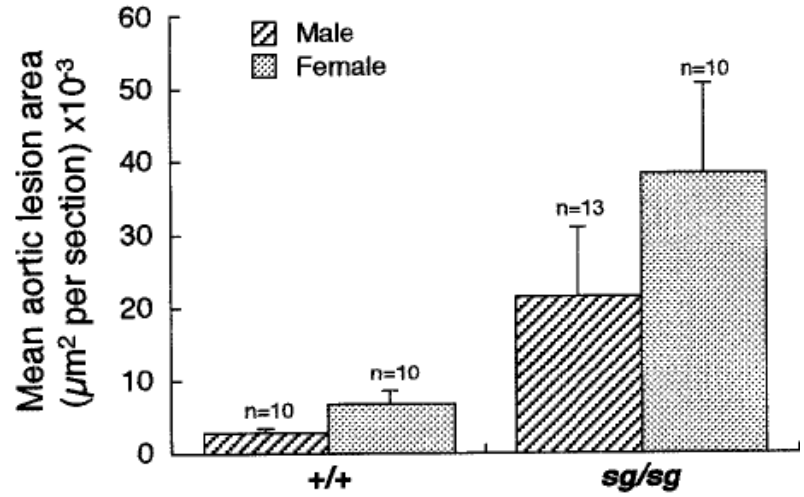
RORα and atherosclerosis

- **RORα deficiency in the sg/sg mice is linked with impairment of lipid metabolism.**
  * **RORα activates expression of apoA-I and apoC-III genes (direct regulation of triglyceride metabolism and HDL formation).**
- **RORα exerts antiinflammatory activities through inhibition of the NFkB signaling pathway.**

RORα is an antiatherogenic factor



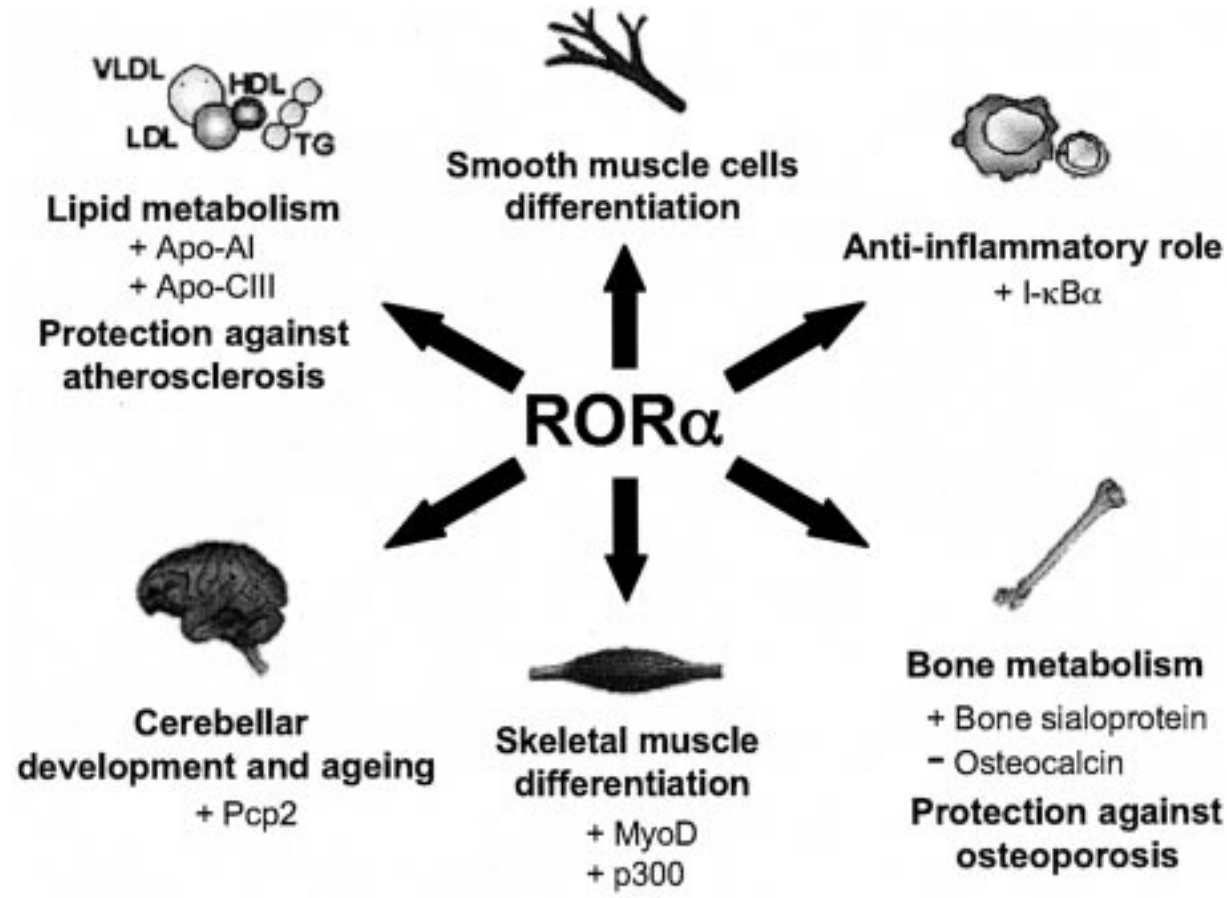




RORα

- **RORα interacts as a monomer (more often) or as a homodimer at direct repeats (DR2) sites.**

- **ROR is a widely expressed nuclear receptor, present in:**
  - *** brain (especially in cerebellar Purkinje cells)**
  - *** thymus**
  - *** skeletal muscle**
  - *** skin,**
  - *** heart**
  - *** vessels**
  - *** liver,**
  - *** lung**
  - *** gut**
  - *** kidney tubules**
  - *** whisker follicles**
  - *** pancreas**

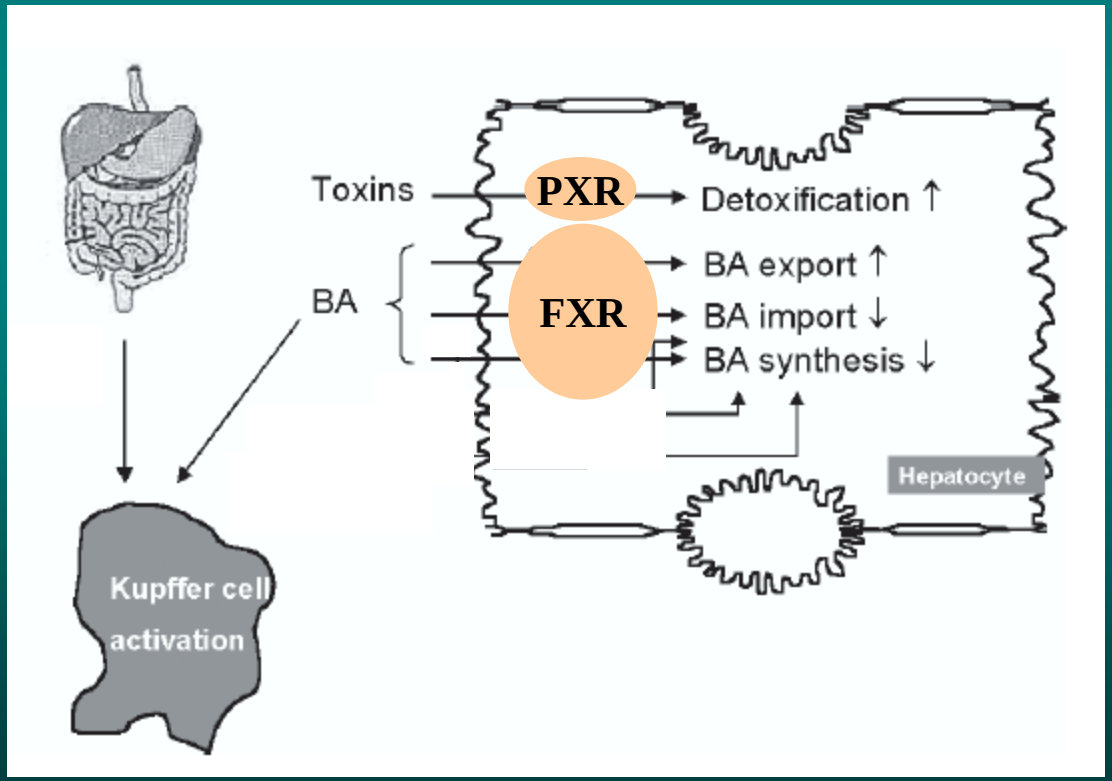


Detoxification

• The efficient detoxification of harmful xenobiotics is essential to the survival of all organisms. Members of the cytochrome P450 (CYP) superfamily of monooxygenases are crucial for the detoxification of most xenobiotics, including various environmental pollutants, carcinogens, and drugs.

• The CYPs are also responsible for the oxidative metabolism of endogenous compounds, including many steroid hormones.

• The CYP3A4 isozyme is of particular significance from a medical perspective because it is involved in the metabolism of roughly 50% of all drugs, including antibiotics, antimycotics, glucocorticoids, statins, tamoxifen, and phytoestrogens.

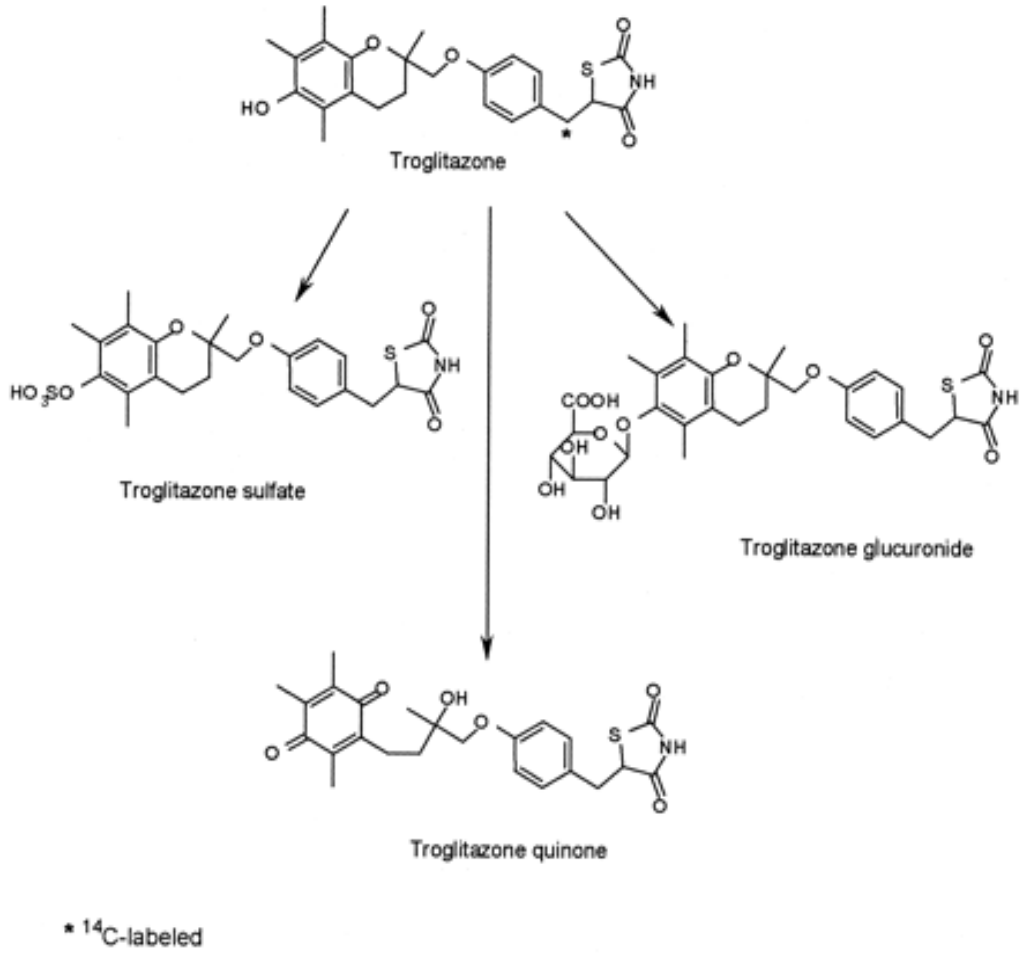


Cytochromes p450

- **Induction of P450s enzymes can alter intestinal and hepatic clearance of drugs and consequently the serum levels of drugs or hormones that are metabolized by these enzyme systems.**

- **Drugs given concomitantly with other drugs or even in combination with plant extracts such as St. John's wort or grapefruit juice have the potential to cause inefficacy of drug treatment or adverse drug reactions, if they activate P450 system.**

- **For example, problems associated with the antidiabetic drug troglitazone could partially be explained by the discovery that it activated PXR in addition to its effect on PPAR. Subsequently, a troglitazone derivative, rosiglitazone, was negatively tested for PXR activation. Rosiglitazone is therefore a much safer compound to use and is the antidiabetic drug of choice today.**

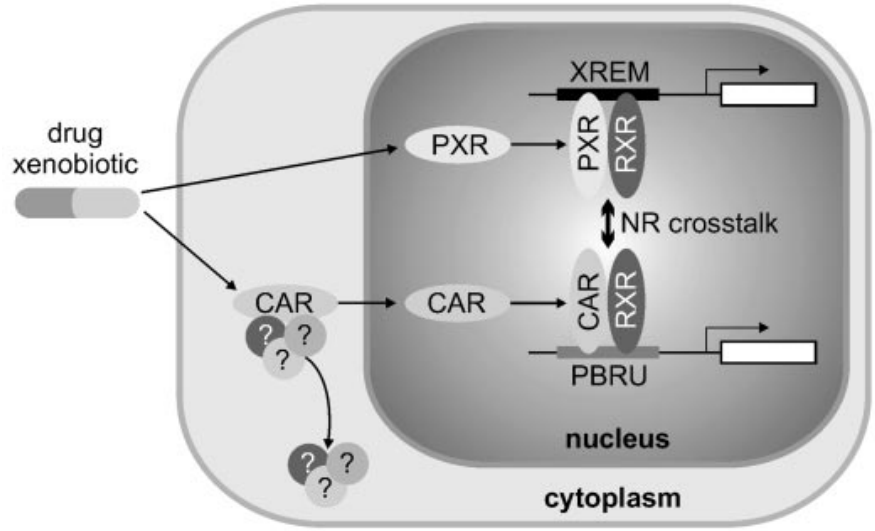


Cytochromes p450

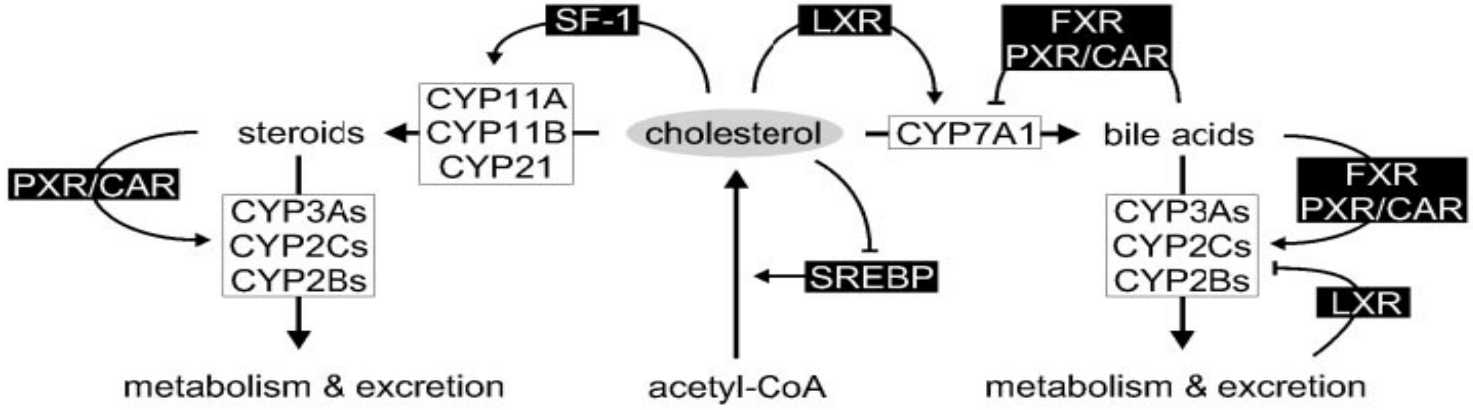
- Nuclear receptors were prime candidates for mediating hepatic drug induction:
  * their ligands are normally small and lipophilic, properties strikingly similar to those of xenobiotic and endobiotic steroids, bile acids, or fatty acids.
  * nuclear receptors bind to DNA elements consisting of repeats of hexamers in different kinds of arrangements such as those found in drug-responsive enhancers of P450s.
  * tissue-specific expression of a subset of nuclear receptors is identical to the tissue specificity of drug induction
  * some nuclear receptors lay key roles in many physiological processes where P450s are involved;

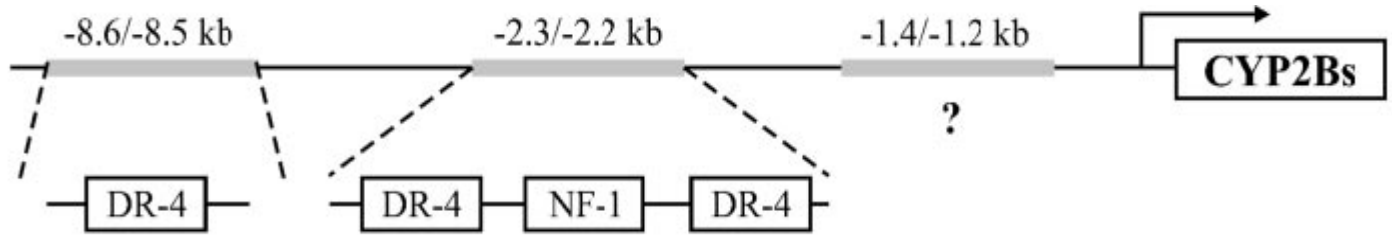
- After entering the cell, xenobiotics and other activators either 1) trigger cytoplasmic-nuclear translocation of CAR by promoting the release of so far unknown proteins, or 2) directly activate PXR in the nucleus.

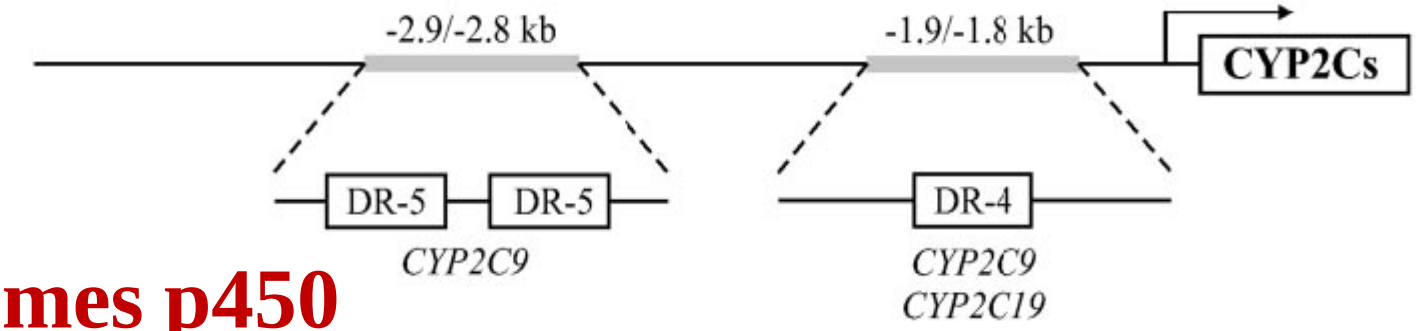
- Subsequently, both PXR and CAR heterodimerize with RXR, bind to their respective response elements, and increase transcription of target genes. In the flanking regions of several genes, response elements have been found that are activated by both PXR and CAR and thus allow direct cross talk of these two receptors.

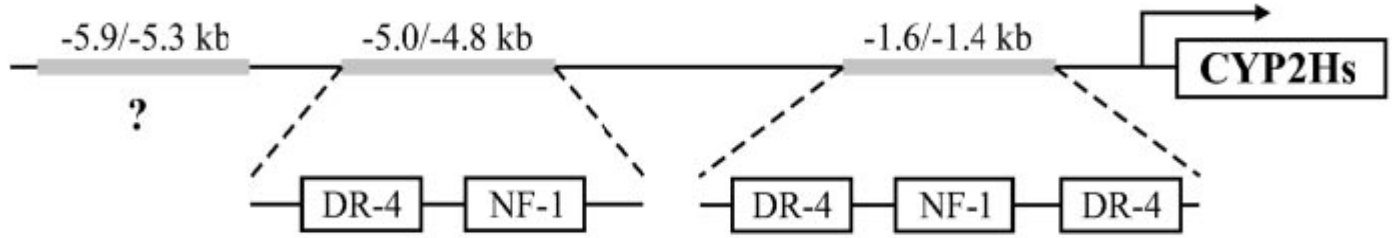


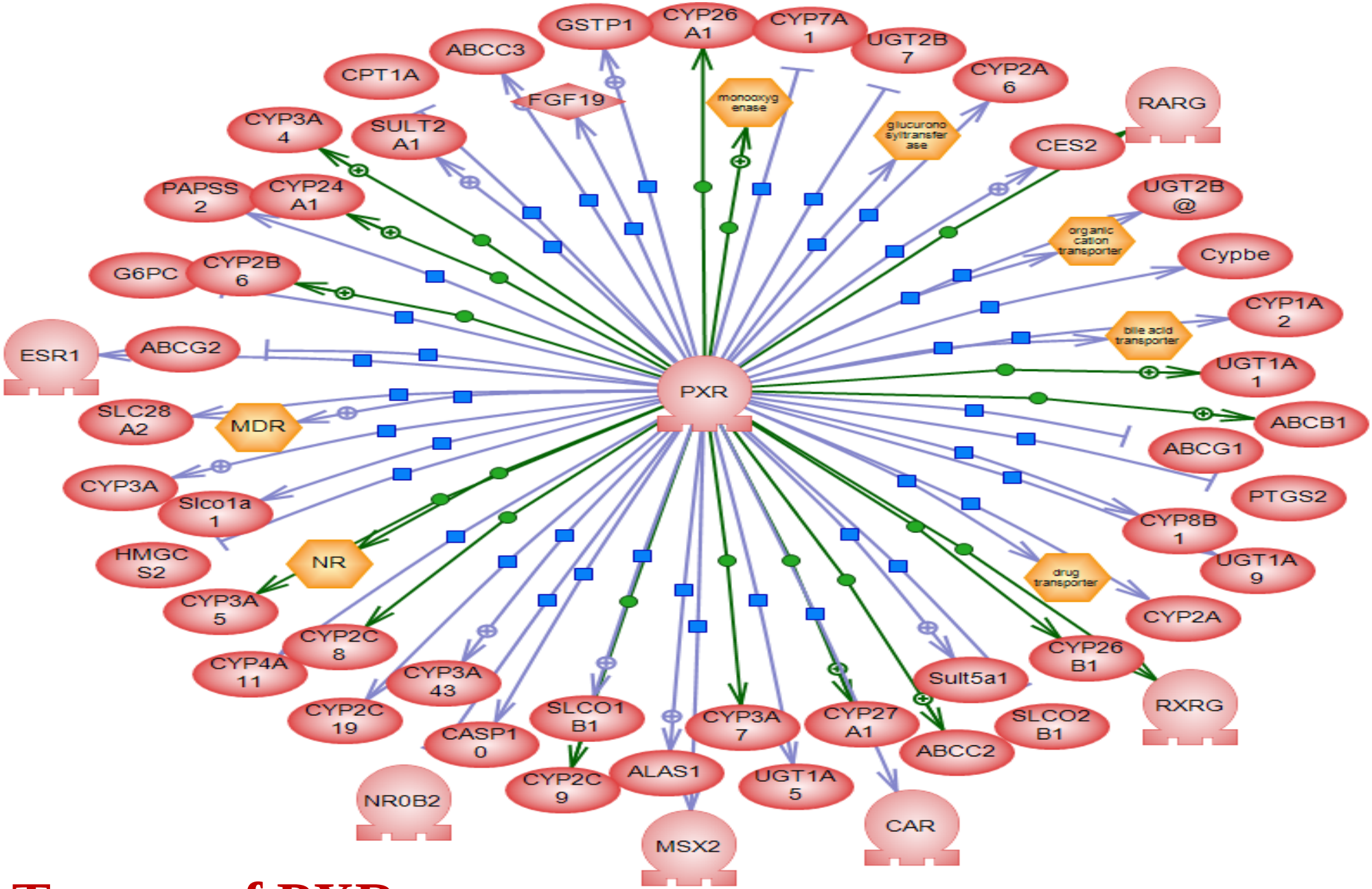
Cytochromes p450











Targets of PXR

Pregnane X Receptor (PXR)

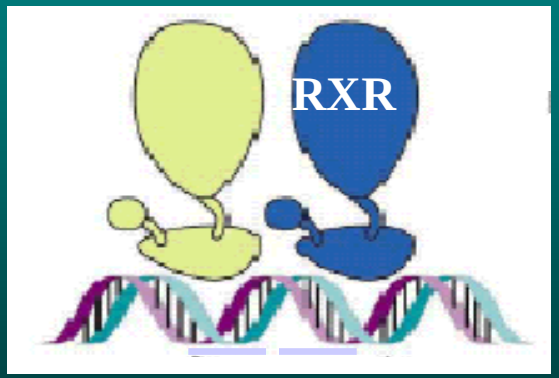
• PXR is predominantly expressed in the liver and intestine and is most closely related to the VDR at the structural and amino acid sequence levels.

• PXR recognize DR-3 motif as a heterodimer with RXR, and is responsible for the activation of the CYP3A4, CYP3A3, CYP3A23 and cholesterol 7a hydroxylase promoters.

• Naturally occurring steroids have been identified that are efficacious activators of PXR. The most potent compounds are C21 steroids (pregnanes) such as the progesterone metabolite 5b-pregnane-3,20-dione, but corticosteroids and estrogens also activate PXR.

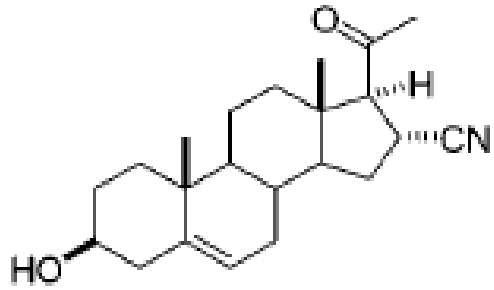
• Thus, in addition to serving as a xenobiotic sensor, PXR is also likely to have important implications in the regulation of steroid homeostasis.

• In patients on steroid replacement therapy, or women taking oral contraceptives, activation of PXR leads to rapid depletion of administered steroids.

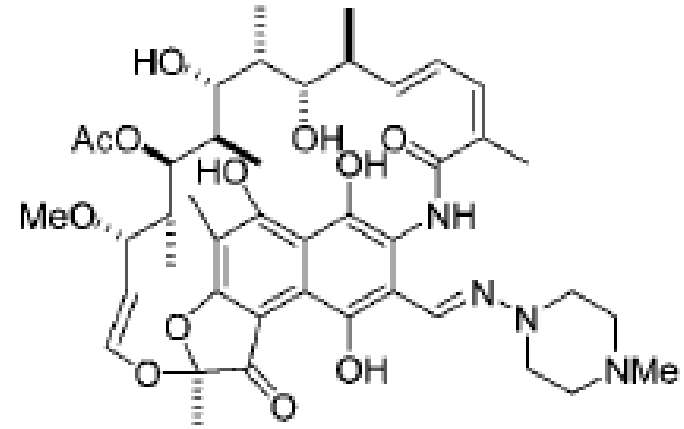


• PXR induces multidrug resistance gene MDR-1 (important in drug resistancy in treatment of tumors) and inducible nitric oxide synthase iNOS (induction of inflammation and contribution to septic shock).

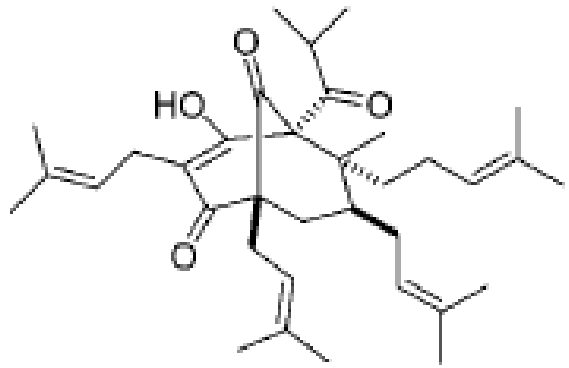
Pregnane X Receptor (PXR) ligands



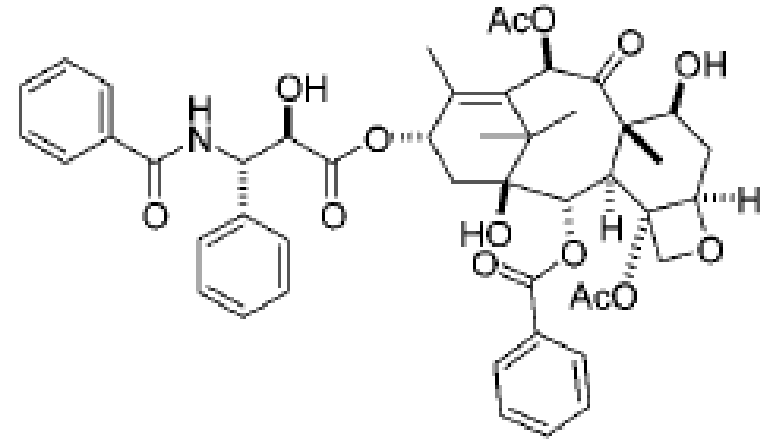
PCN



rifampicin



hyperforin



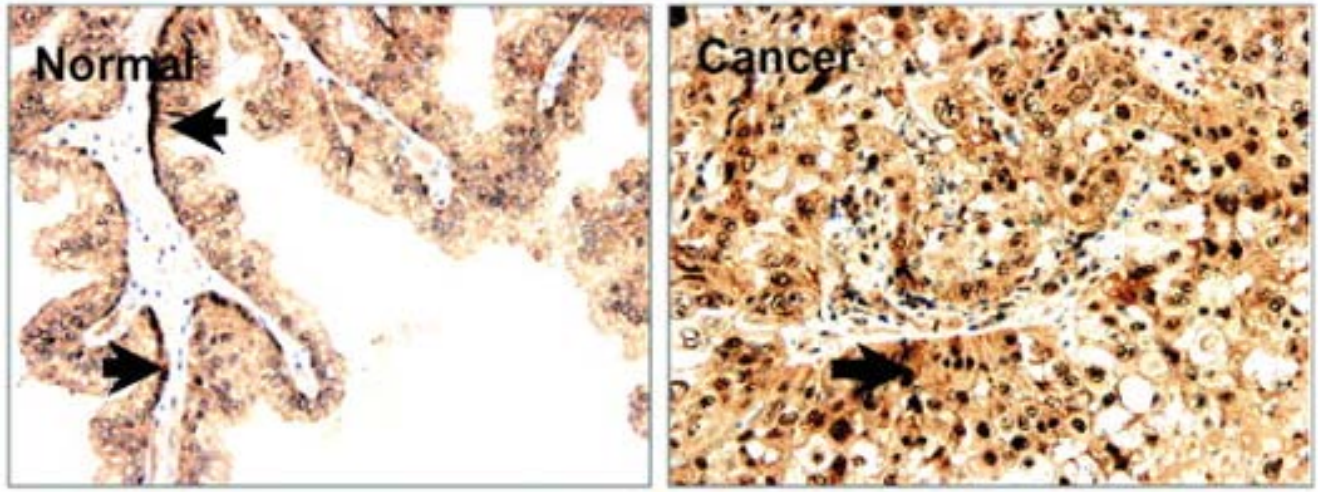
paclitaxel

Pregnane X Receptor (PXR)

- PXR (cloned in 1998) can be activated by an impressive array of structurally diverse molecules, ranging from xenobiotics to steroids.

- The name 'pregnane' X receptor derives from activation of the receptor by pregnane (21-carbon or C21) steroids such as progesterone or 5β-pregnan-3,20-dione, although estrane (C18) and androstane (C19) steroids also activate PXRs (another name for PXR is the 'steroid and xenobiotic receptor' or SXR). Receptor is activated both by synthetic steroids and steroid antagonists. Such behavior is uncharacteristic of the classic steroid receptors, thus PXR is an atypical mediator of steroid action.

- In contrast to the classic steroid hormone receptors, high-affinity (subnanomolar) ligands for PXR have not been discovered. The lowest EC50 values of steroids for activating human PXR in reporter gene assays are low micromolar or barely submicromolar, generally at least two to three orders of magnitude higher than concentrations found circulating in plasma.



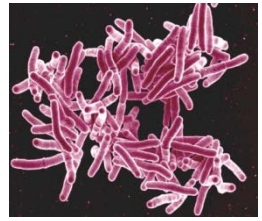
Prostate cancer stained for PXR

PXR and drug-drug interaction

- **Many of the xenobiotics that activate PXR are prescription drugs, including the antibiotic rifampicin, the anti-inflammatory glucocorticoid dexamethasone, the HIV protease inhibitor ritonavir and the cancer drug paclitaxel.**

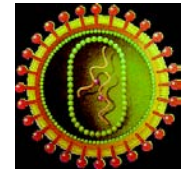
- **Activation of PXR and the subsequent induction of CYP450 and other genes can result in an accelerated metabolism of other medications. CYP3A4 alone is involved in the metabolism of ~50% of all prescription drugs. Thus, drugs that activate PXR have the potential to reduce the clinical efficacy of more than one-half of all other drugs that are coadministered, often with lifethreatening consequences.**

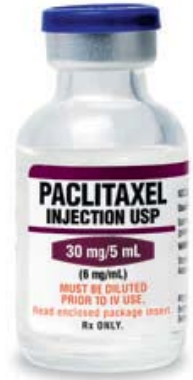
- **Ideally, new drugs would not activate PXR. Now that robust in vitro assays are available to detect PXR activity, it is possible to screen candidate drug molecules prospectively and replace those that activate PXR with chemicals that do not.**



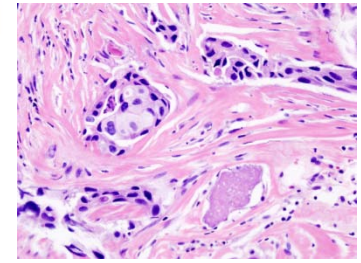
Mycobacterium tuberculosis

HIV

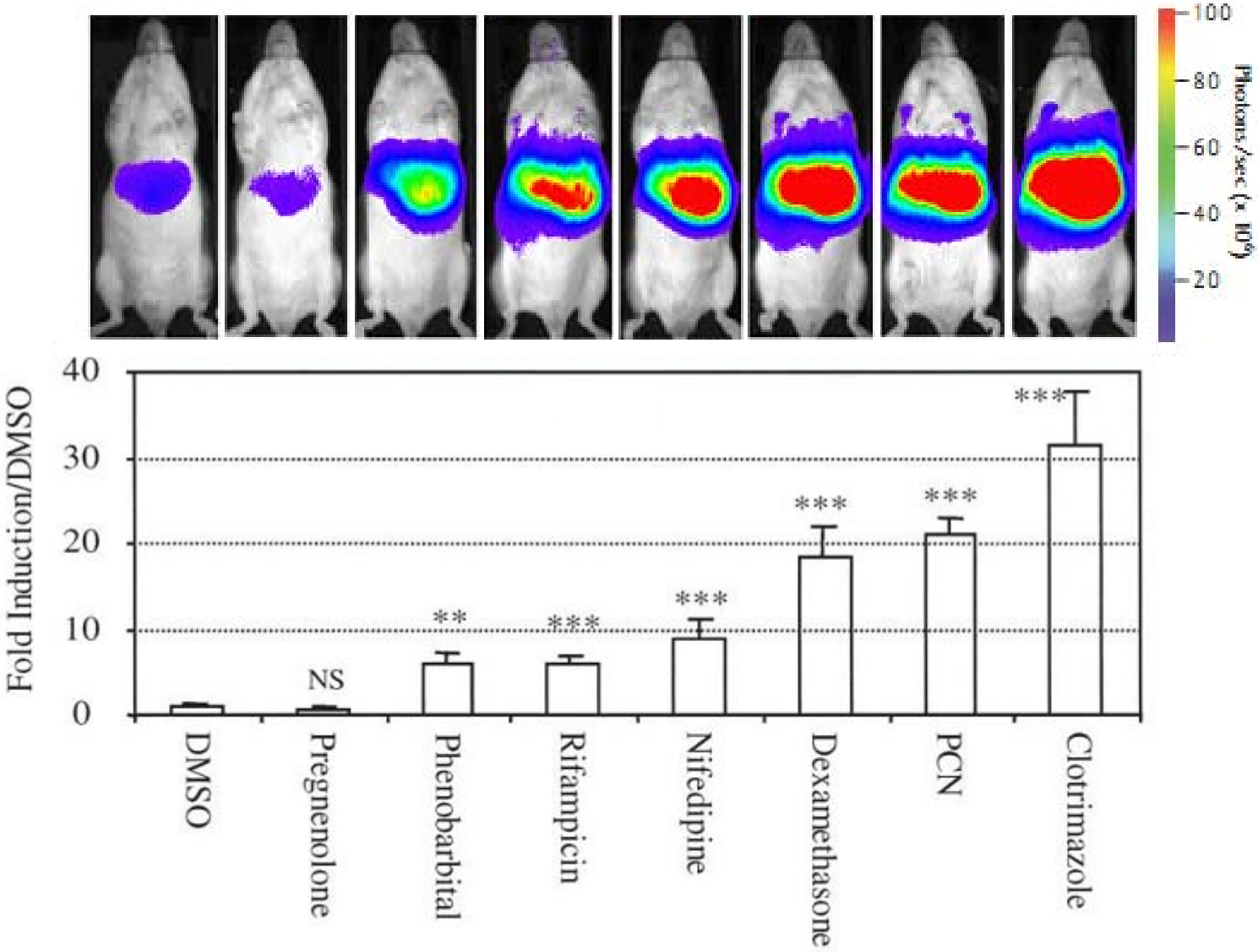




breast carcinoma



Pregnane X Receptor (PXR)



PXR – St. John's wort

- St. John's wort is an herb derived from the flowering plant *Hypericum perforatum* that is widely used to treat mild to moderate depression.

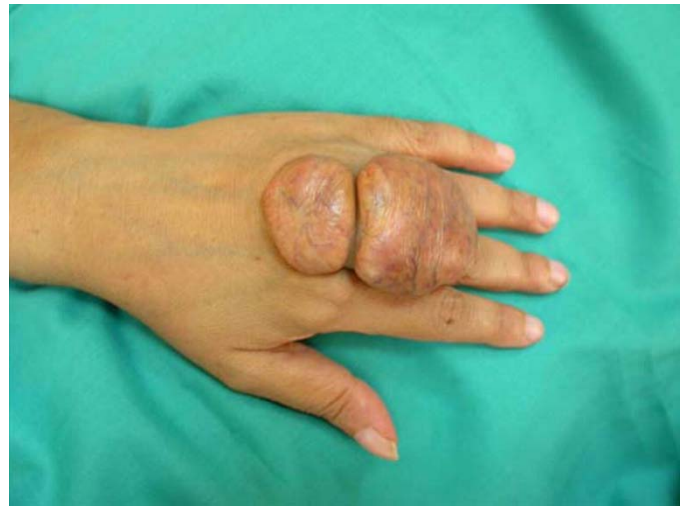
- In the late 1990s, a series of reports appeared describing interactions between St. John's wort and various drugs including oral contraceptives, the immunosuppressant cyclosporin, the HIV protease inhibitor indinavir and the anticoagulant warfarin. In each case, cotreatment resulted in a marked decrease in the effective concentrations of the prescription drug, often with life-threatening consequences.

- Commercial preparations of St. John's wort activate PXR in cell-based reporter assays and induce CYP3A4 expression in hepatocytes. St. John's wort is a complex mixture of about two dozen different chemicals, among them hyperforin is the high affinity ligand of PXR.

PXR – cerebrotendinous xanthomatosis

-The importance of PXR in bile salt metabolism and elimination is illustrated by the rare disease cerebrotendinous xanthomatosis (CTX), an inborn error of metabolism caused by deficiency of CYP27A1.

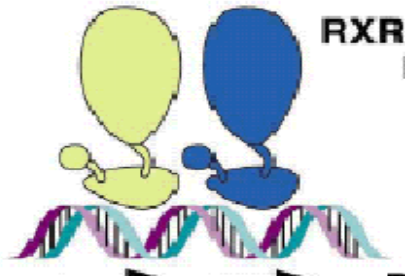
- In humans, the enzyme deficiency of CTX leads to accumulation of C27 bile alcohols (which retain the entire carbon skeleton of cholesterol) and the pathological symptoms of xanthomas, gallstones, and neurological dysfunction. Individuals with CTX are unable to prevent pathological accumulation of 5β-cholestan-3α,7α,12α-triol and other bile acid precursors.

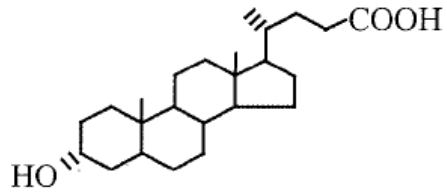


cerebrotendinous xanthomatosis

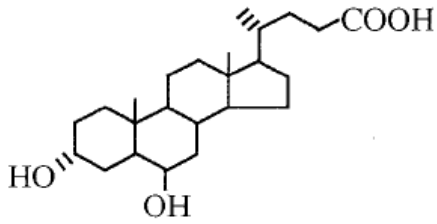
PXR – bile salts as ligands

- **Bile salts such as cholic acid are the endproducts of cholesterol metabolism and also solubilize lipophilic compounds in the gut. They are synthesized in the liver and stored in the gallbladder (in those animals that have this organ), and are generally not toxic even when micromolar concentrations accrue in the circulating plasma. An exception is lithocholic acid (3α-hydroxy-5β-cholan-24-oic acid), a mono-hydroxylated 'secondary' bile acid formed by the action of bacterial 7-dehydroxlases on primary bile acids such as chenodeoxycholic acid. High levels of lithocholic acid are cytotoxic and implicated as a factor in colon cancer.**

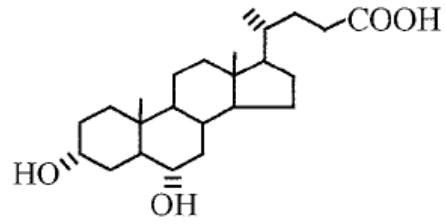




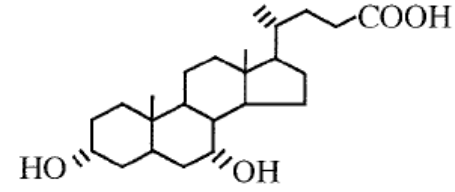
lithocholic acid



murideoxycholic acid (6β)



hyodeoxycholic acid (6α)

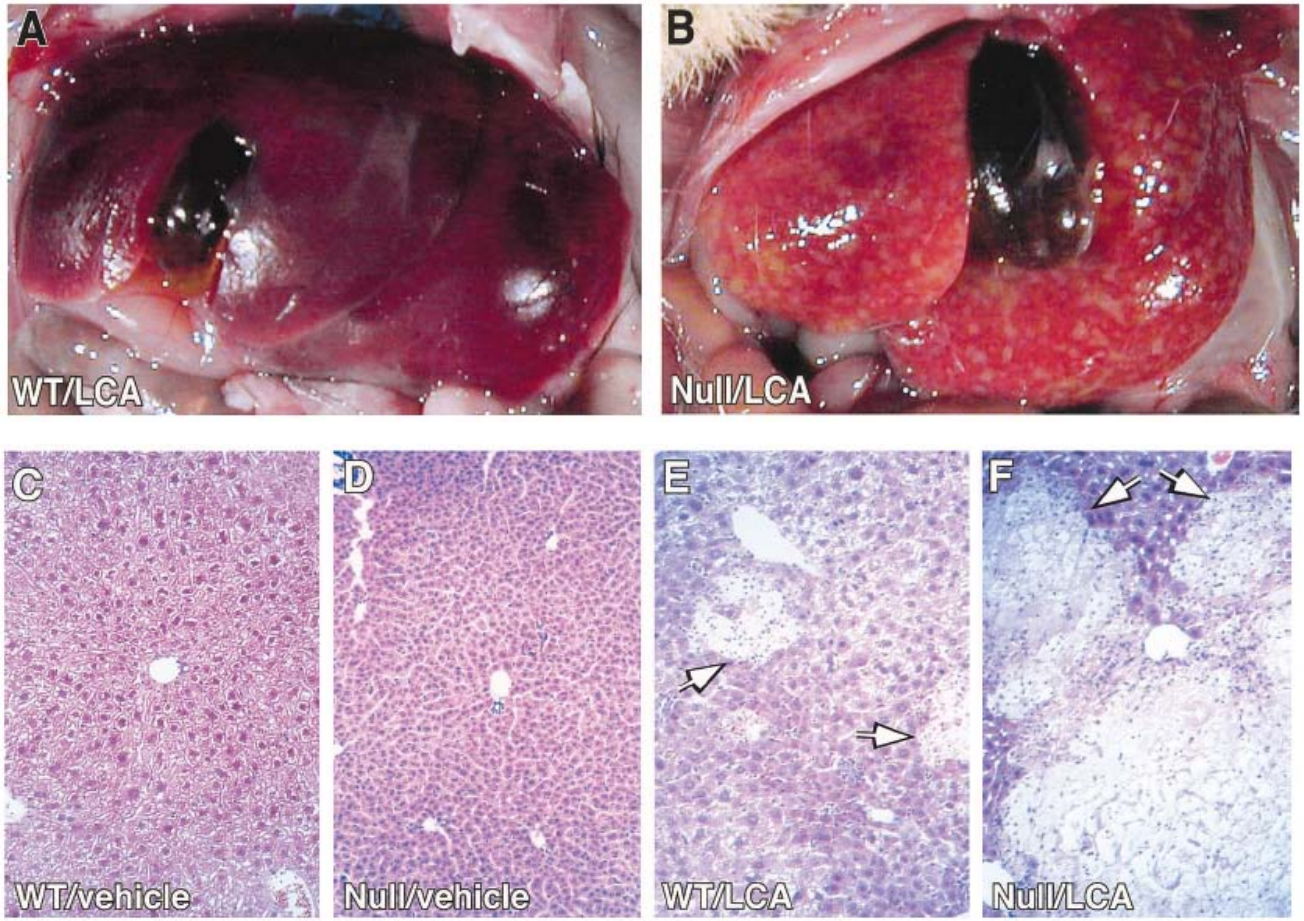


chenodeoxycholic acid (7α)

Pregnane X Receptor (PXR)

-Exogenous steroids and pharmacologic substances may modulate the expression of cytochrome P450 enzymes that would protect against subsequent exposure to toxic LCA.

- Mice that lack PXR do not have any overt phenotype under standard laboratory conditions, but their response to xenobiotics is severely compromised.



LCA-mediated liver damage in wild type and PXR null mice.

LCA – lithocholic acid

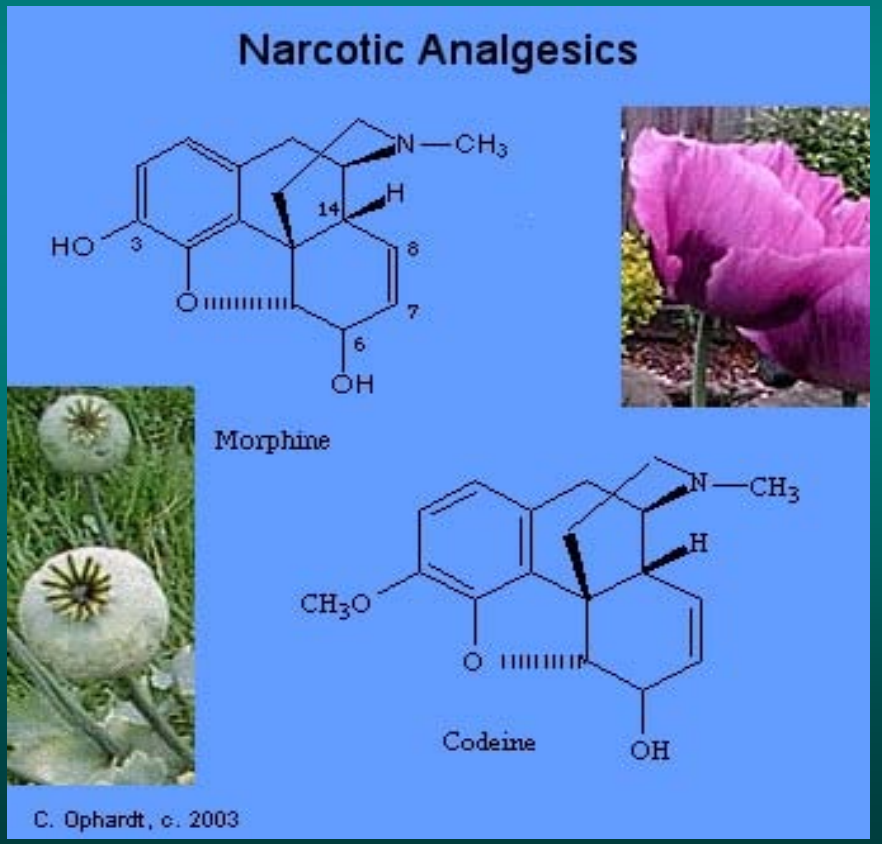
Molecular diagnostic-based therapies

- Codeine, a commonly used analgesic, must be converted from an inactive form to the active form (morphine) by the CYP2D6 enzyme for a therapeutic effect to occur.

* Patients with a polymorphism leading to increased production of CYP2D6 are ultra-rapid metabolizers of codeine and are more likely to develop adverse effects and toxicity when taking a standard dose of codeine, including impaired breathing and sedation.

- Patients with decreased CYP2D6 production are poor metabolisers and will show little or no conversion of codeine to morphine; they will not experience any pain relief, but will become nauseated due to the higher amounts of codeine in their body.

- Frequency of CYP2D6 alleles varies in different ethnic groups:
* 7% of Caucasians may have a defective CYP2D6 gene, resulting in reduced pain relief due to poor metabolism of the drug.

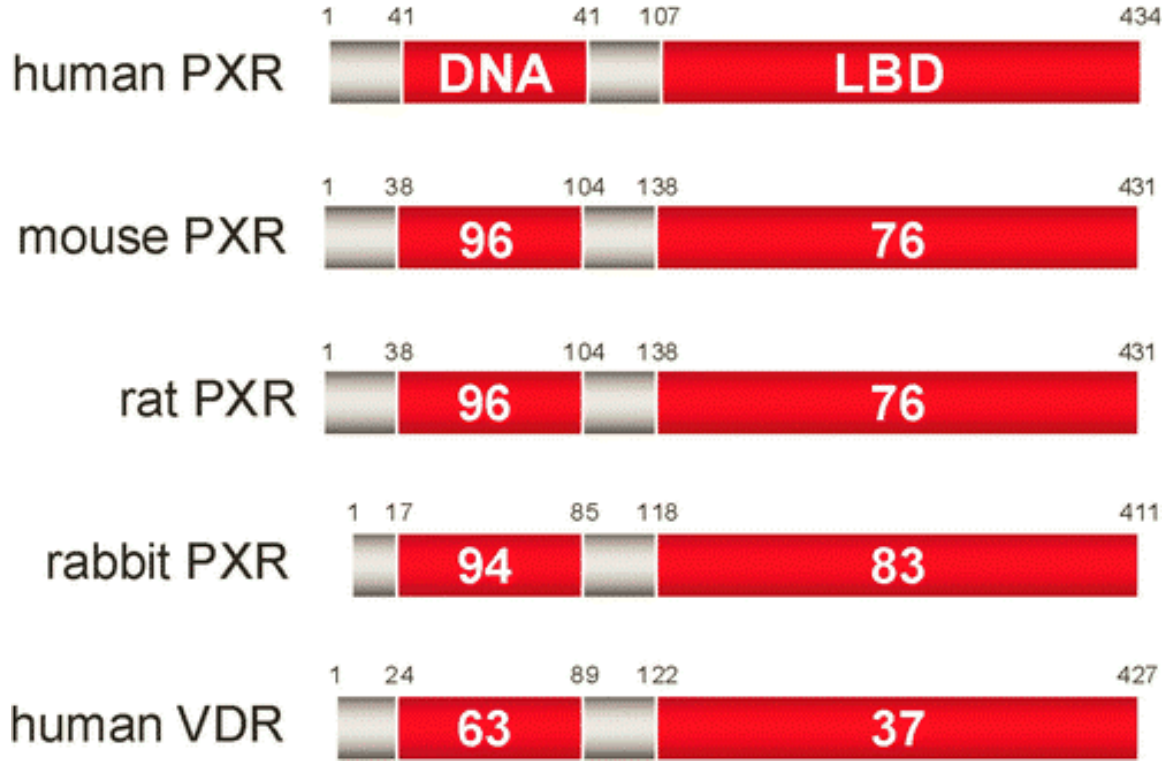


PXR – genetic variation in humans

- Mutations in the PXR coding region are quite rare, although variation in non-coding regions or due to splice variants may have clinical importance. PXR gene showed nucleotide diversity lower than the genome-wide average for human genes and no aminoacid changing mutations in the LBD.

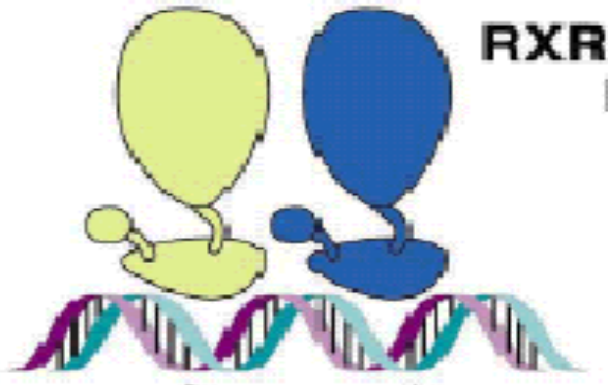
- Sequence differences in the coding region of PXR do not account for well-described interindividual differences in metabolism, such as variation in baseline activity or inducibility of CYP3A4 in liver or intestine.

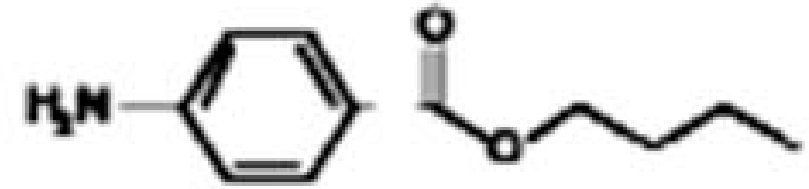
- Sequence divergence is also low between human, chimpanzee, and rhesus monkey PXRs.



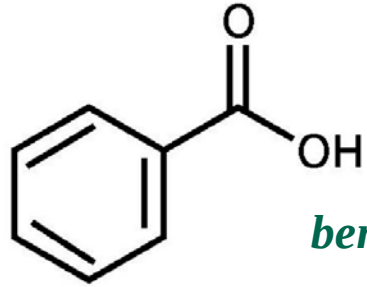
Benzoate X Receptor (BXR) – adopted orphan receptor

- **BXR (known also as ONR-1) heterodimerizes with RXR and binds high-affinity DNA sites composed of a variant thyroid hormone response element.**
- **BXR:RXR heterodimers bind preferentially to direct repeats of the sequence AGTTCA separated by four nucleotides (DR4).**
- **Recently, alkyl esters of amino and hydroxy benzoic acids were identified as potent, stereoselective activators. These molecules act as bona fide ligands.**
- **Benzoates comprise a new molecular class of nuclear receptor ligand and their activity suggests that BXR may control a previously unsuspected vertebrate signaling pathway.**





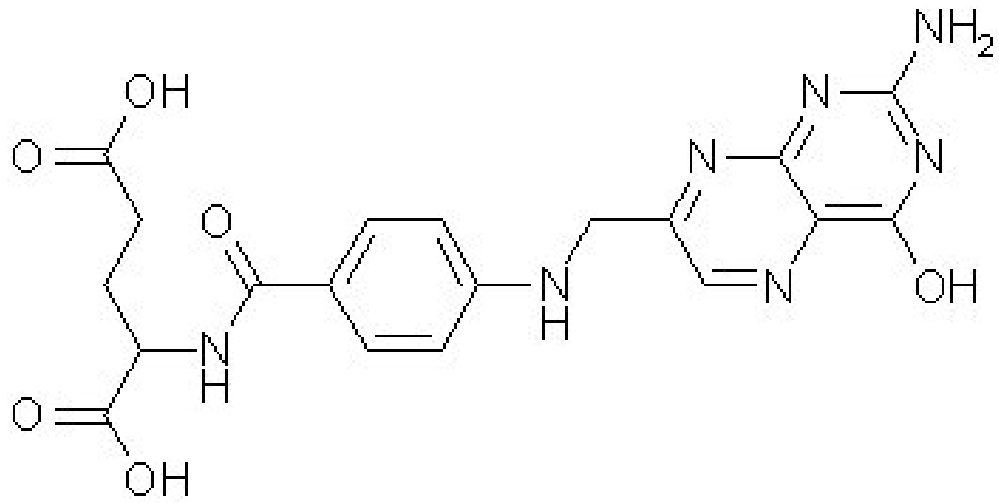
4-amino-butyl benzoate



benzoic acid

Benzoates

- **The endogenous benzoates are related to the nutrient *p*-amino benzoic acid (PABA), an integral component of the essential B-vitamin folic acid, suggesting a potential connection between nutrition and development.**
- **Interestingly, folate lowers blood levels of homocysteine, which in high levels has been linked to heart disease and hypertension.**
- **This further suggests a connection between folate metabolism and BXR activation.**

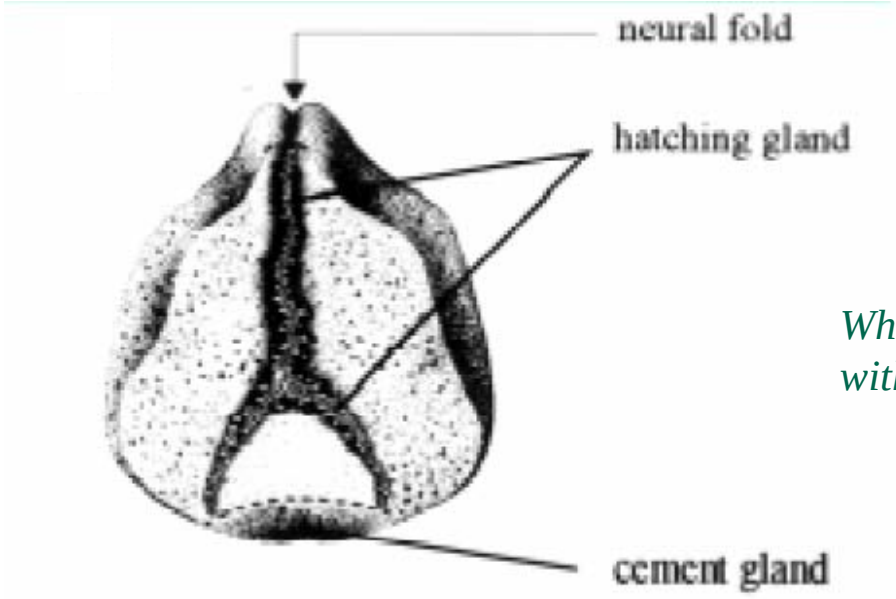


folic acid

BXR

- The identification of nuclear receptors and their ligands in the pre-gastrula embryo, long before any organs have formed, suggests that the classic endocrine paradigm is not operative in early development.

- Instead, it appears that the ligands either diffuse from their point of origin to neighboring cells (paracrine signaling) or perhaps act within the cells where they are synthesized (autocrine signaling).



Whole-mount in situ hybridisation of Xenopus laevis embryo with a BXR probe

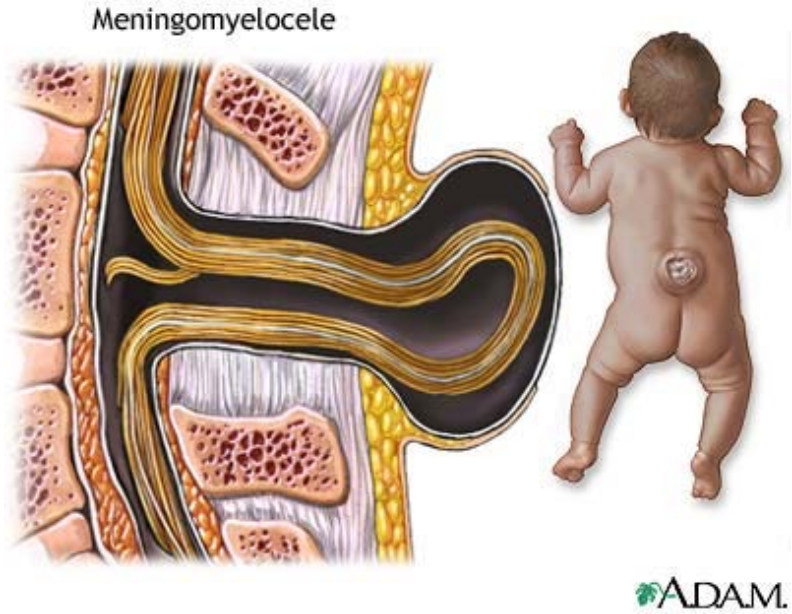
Spina bifida

- Developmental birth defect caused by the incomplete closure of the embryonic neural tube (normally the closure occurs around 28 days after fertilization).

- Lack of folic acid is a contributing factor in the pathogenesis of neural tube defects, including spina bifida. Supplementation of the mother's diet with folate can reduce the incidence of neural tube defects by about 70 percent, and can also decrease the severity of these defects when they occur.

- The most common location of the malformations is the lumbar and sacral areas. Meningomyelocele is the most significant form and it is this that leads to disability in most affected individuals - the outer part of some of the vertebrae are not completely closed. The split in the vertebrae is so small that the spinal cord does not protrude. The skin at the site of the lesion may be normal, or it may have some hair growing from it.

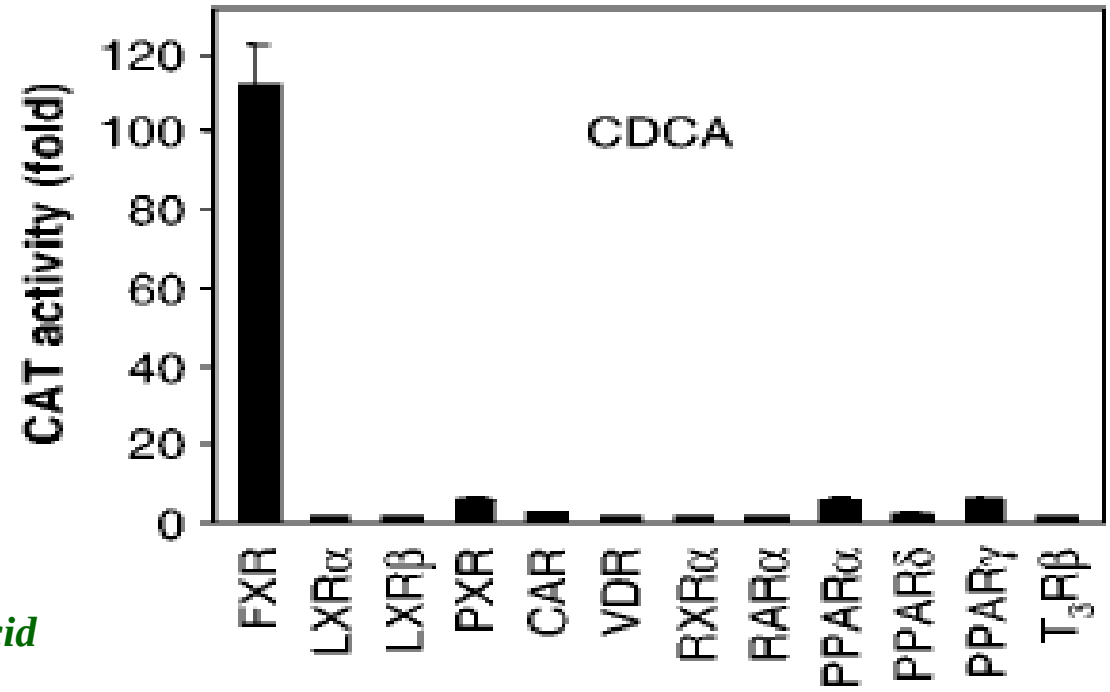
- Spina bifida can be surgically closed after birth, but this does not restore normal function to the affected part of the spinal cord. Intrauterine surgery for spina bifida has also been performed.



Detoxification

- **Cholesterol homeostasis is achieved through the regulation of dietary cholesterol uptake, endogenous biosynthesis, and the disposal of cholesterol in the form of bile acids.**

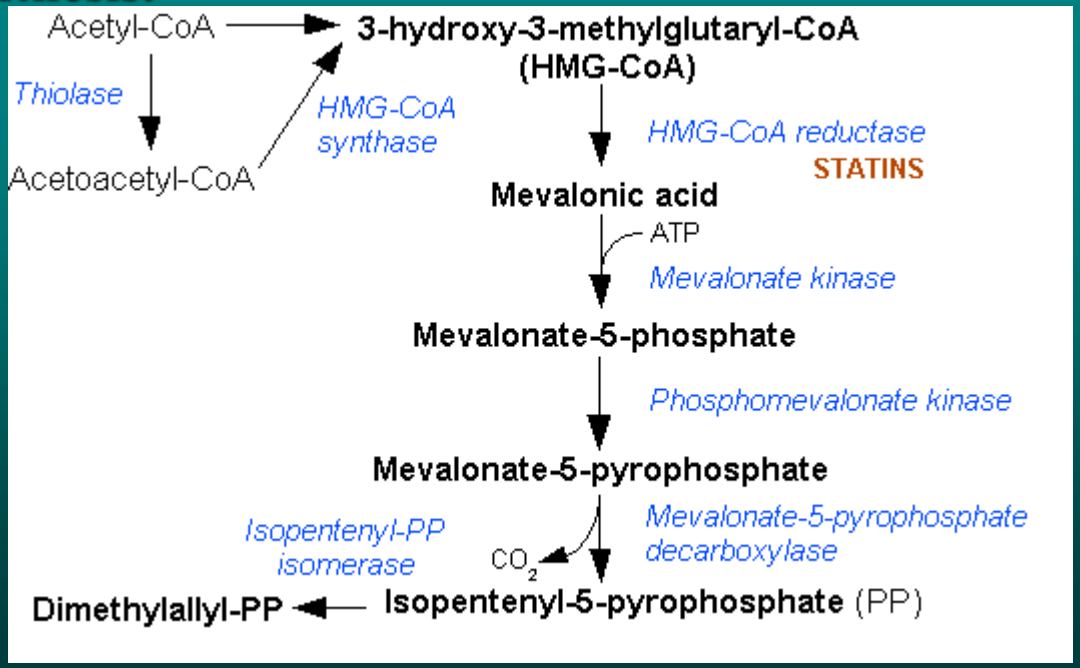
- **Bile acids are not simply metabolic by-products, but are essential for appropriate absorption of dietary lipids and also regulate gene transcription. Among the genes regulated by bile acids are:**
  - *** cholesterol 7a-hydroxylase (Cyp7a), the rate-limiting enzyme in bile acid biosynthesis**
  - *** intestinal bile acid–binding protein (I-BABP), a cytosolic protein that serves as a component of the bile acid transport system in the ileal enterocyte.**



CDCA - chenodeoxycholic acid

FXR (Farnesoid X Receptor)

- FXR binds in a complex with RXR (activation of expression) or act as homodimer (inhibition of expression)
- FXR can be activated by high concentrations of farnesol. Farnesol is an isoprene intermediate in the mevalonate biosynthetic pathway and most likely activates FXR via its conversion into a higher affinity derivative.
- FXR was shown to be a receptor for bile acids (higher affinity than for farnesol).
- FXR is a general regulator of bile acid metabolism, acting through suppression of CYP7A to reduce synthesis.

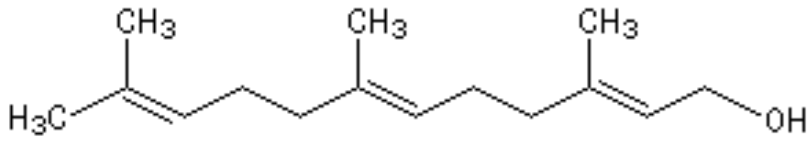


FXR (Farnesoid X Receptor)

- FXR was first identified as a rat orphan receptor which could be activated by high concentrations of farnesol,

- The mouse ortholog of FXR (RIP14), is only poorly activated by farnesoids but robustly by retinoic acid and the synthetic retinoid agonist TTNPB and retinoic acids. This activation requires, however, supraphysiological concentrations of activators, suggesting that they are unlikely to act as direct ligands.

- This raises the possibility that either an unidentified retinoid metabolite is the endogenous FXR ligand, or that both retinoids and farnesoids are mimicking the activity of an authentic ligand, perhaps another retinoid or terpenoid. Thus, FXR is either the next retinoid receptor or a novel terpenoid receptor.



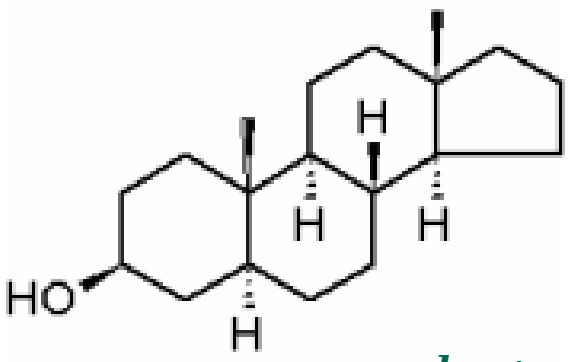
farnesol

CARβ – a ligand inactivated receptor

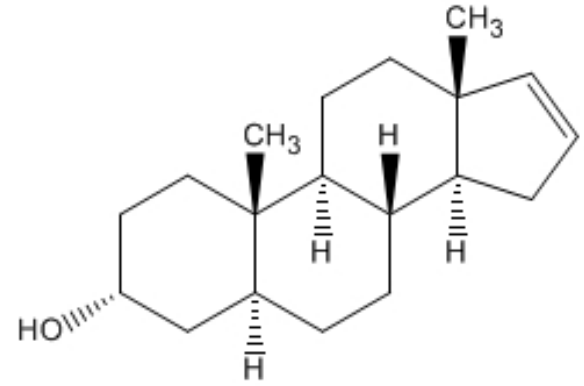
- CARβ was found to be constitutively active on DR-5 response elements. This could be the result of the production of an endogenous intracellular ligand or inherent activity in an unliganded state.

- Androstanol and androstenol are selective transcriptional inhibitors of CARβ. These androgens completely lack activity on the androgen receptor whereas classic androgens such as testosterone fail to act on CARβ.

- Although CARβ-specific androstanes are related to mammalian pheromones, the CARβ expression pattern makes it unlikely to participate in this process.



androstanol



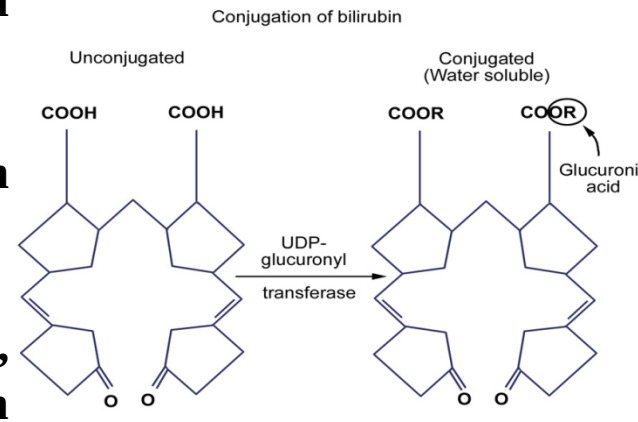
androstenol

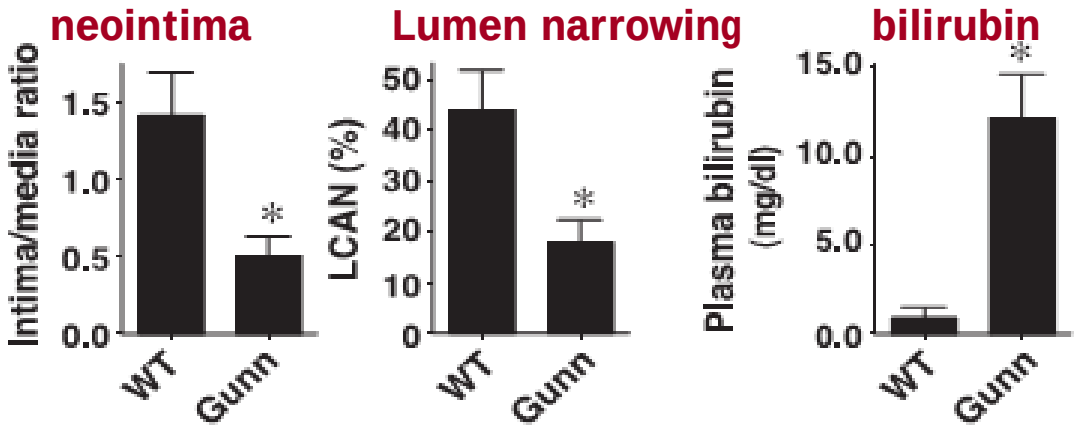
CARβ – activator of UGT expression

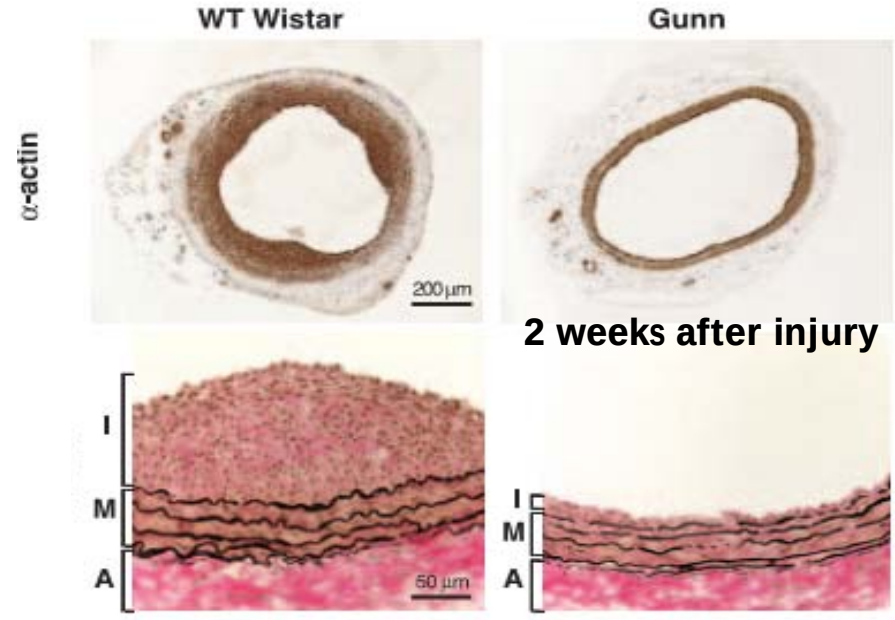
- UDP-glucoronyl transferase (UGT) is a direct target for hPXR and CAR.

- Low activity of UGT leads to hyperbilirubinemia and have been implicated in carcinogenesis.

- The carcinogenic potential of this gene was suggested in the Gunn rat, where a mutation in the *UGT1 allele* leads to a decrease glucuronidation of the carcinogenic benzo-(a)pyrene, leading to elevated levels of DNA adducts. Environmental mutagens, such as benzo(a)pyrenes, have been identified as substrates for several UGT1 proteins.







Gunn rats are protected from atherosclerosis

COUP-TF

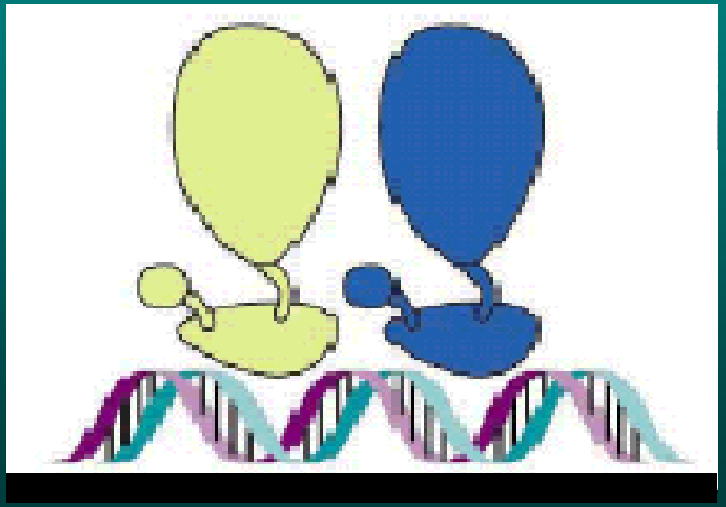
(chicken ovalbumin upstream promoter transcription factor)

COUP-TFα was initially identified as a transcription factor required for expression of the chicken ovalbumin gene.

It acts as **homodimer** but can also form **heterodimeric** complexes with **RXR**. Still **orphan**.

During murine development, COUP-TFs are preferentially expressed in the central nervous system. COUP-TFα plays a crucial role in the **development of the peripheral nervous system**. **COUP-TFα** null mice have difficulties in suckling and swallowing and die shortly after birth apparently from starvation and dehydration.

COUP-TFβ null mutants die in utero around 10 d.p.c. due to defect in angiogenesis, vascular remodeling, and heart development.

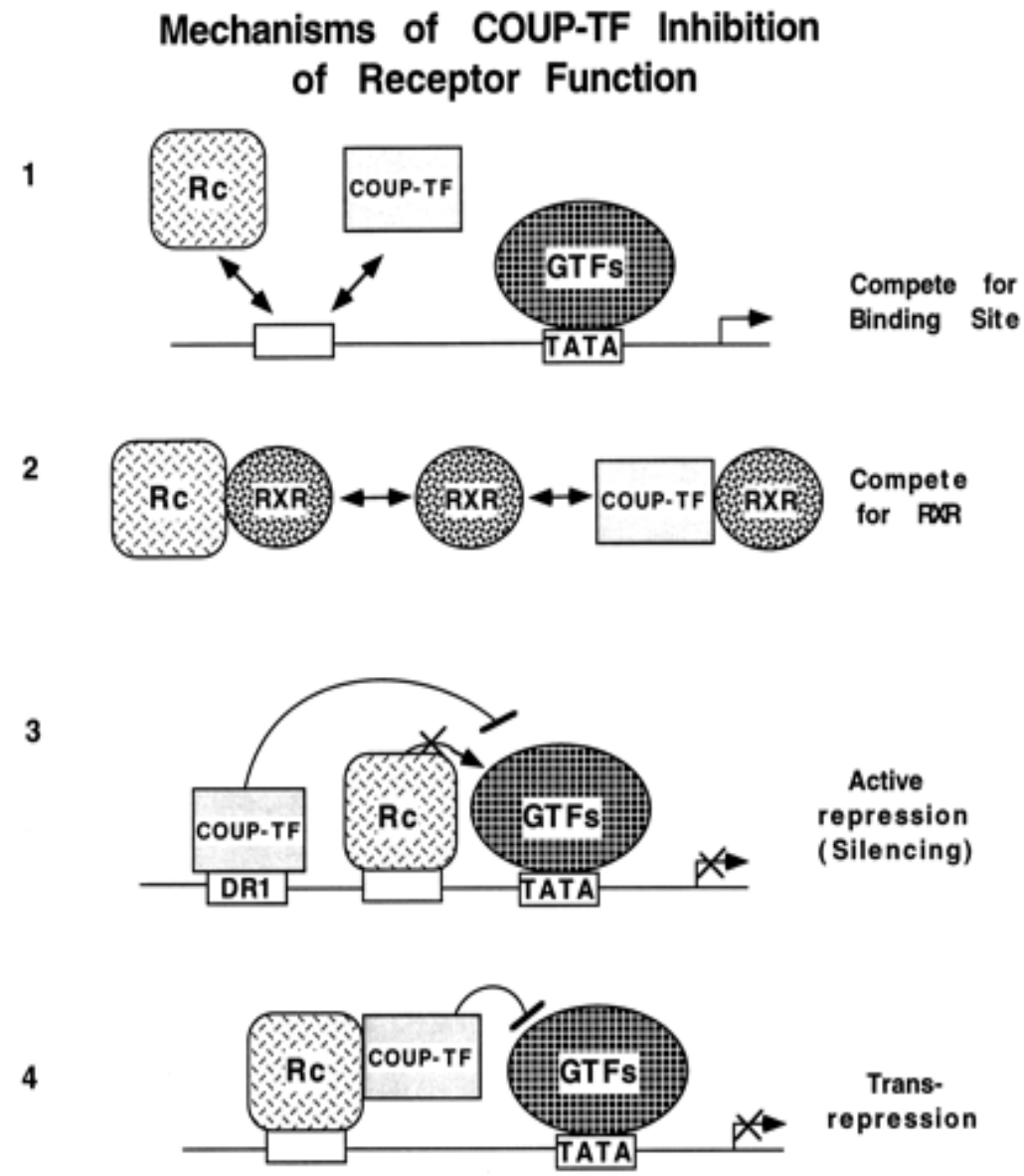


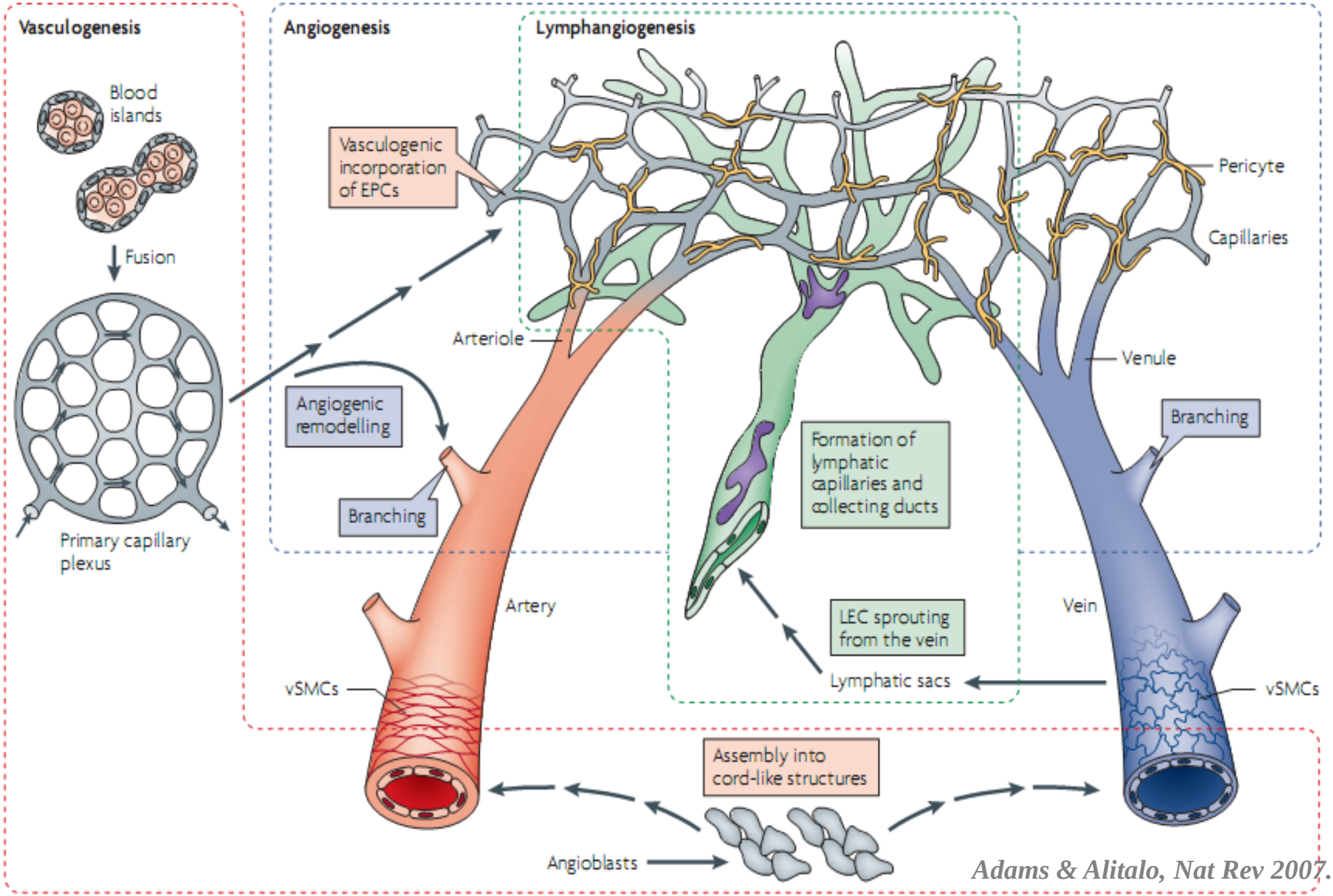
COUPF-TF (chicken ovalbumin upstream promoter transcription factor)

- **Ubiquitously expressed.**

- **COUP-TF repress several nuclear hormone signaling pathways by competition with other nuclear receptors for binding to their response elements. It can act as:**
  - *** homodimer**
  - *** heterodimer with the RXR**

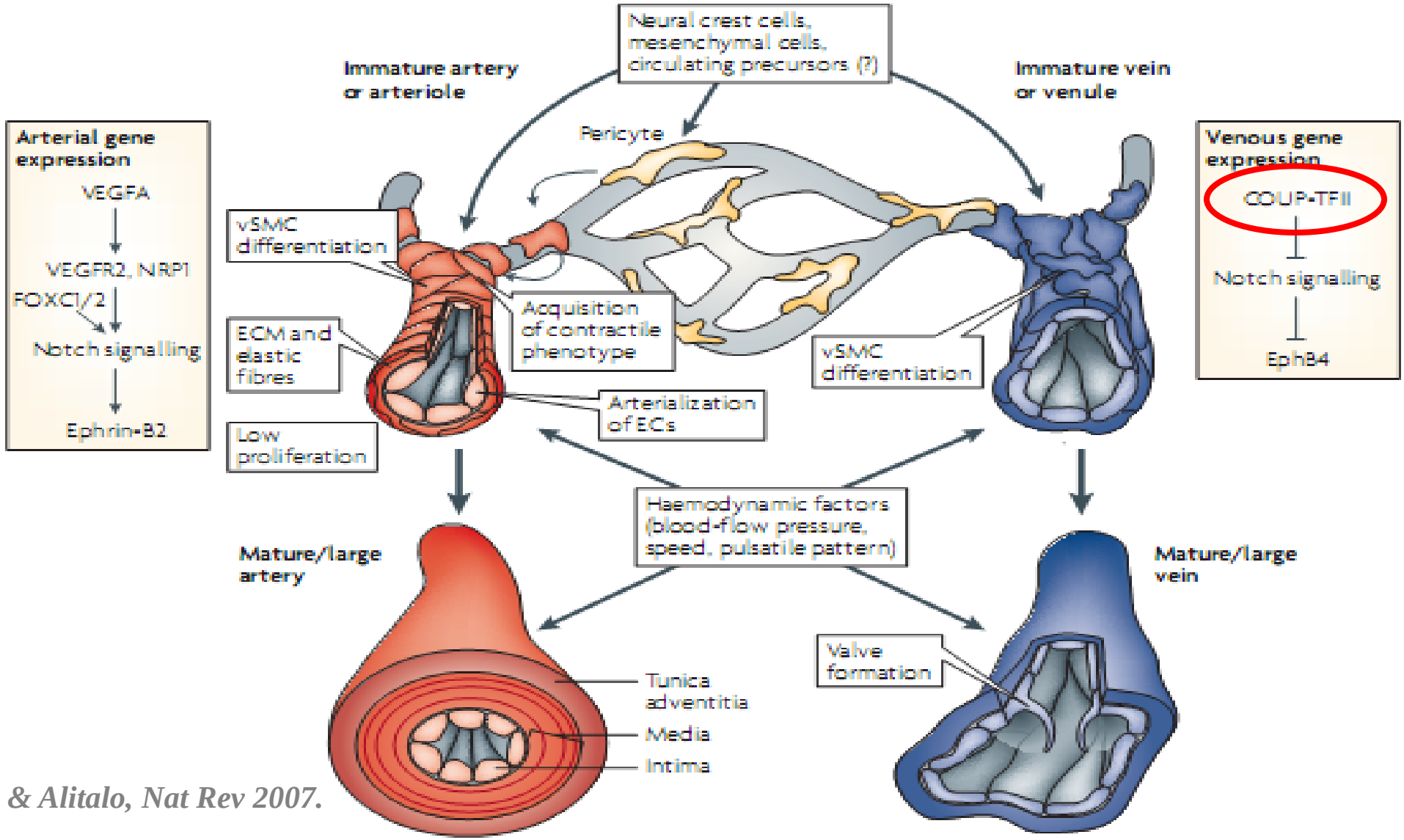
- **In contrast to the other members of the nuclear receptor superfamily, COUP-TF does not show a clear response element preference.**





Adams & Alitalo, Nat Rev 2007.

COUP-TFII is expressed in venous endothelium and functions upstream of arteriovenous decision-making process.
*** Lack of COUP-TFII: veins acquire arterial characteristics (e.g. ephrin-B2 expression)**
*** Overexpression of COUP-TFII: arterial endothelial cells lose arterial markers and start to express venous genes (e.g. EphB4)**



Adams & Alitalo, Nat Rev 2007.

Thank you ☺ and see you next week (?)