Ch 3 – L 4.3

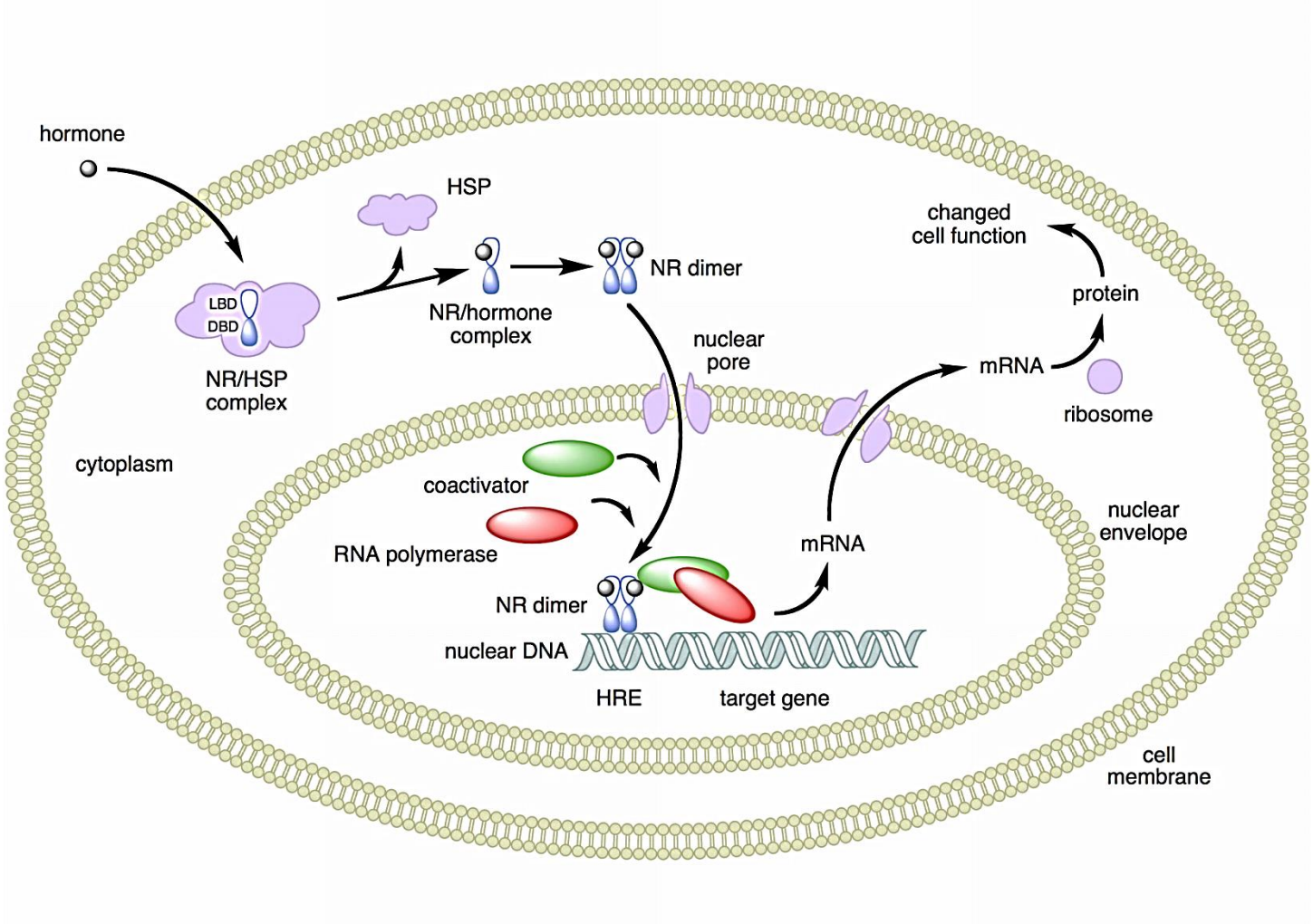
Corepressors

What about NEGATIVE control?

It is known that TFs can be either activators or repressors
(*even more: the same TF may behave as A or R depnding on the E/P context*)

Example from the Nuclear Receptor (NR) superfamily
(*includes steroid hormone receptors*)

In **Human most of the** the genes responding primarily (protein synthesis- -independent) to steroid hormones are of this kind.
Let's consider the Nuclear Receptor Superfamily of Transcription Factors



Nuclear Receptor activity, Type I and Type II, orphan receptors

Nuclear Receptor are a class of TFs that have been intesively studied

Dysfunction of nuclear receptor signalling leads to proliferative, reproductive and metabolic diseases such as cancer, infertility, obesity and diabetes. Therefore:

Nuclear receptors are very important as **drug targets**

Pharmaceutical nuclear receptor **agonists** or **antagonists** are used in human therapy. Most known examples:

◊ tamoxifen for oestrogen receptors (targeted in breast cancer),

◊ flutamide-bicalutamide for androgen receptor (prostate cancer)

◊ thiazolidinediones for peroxisome proliferator-activated receptor-γ (PPARγ) (targeted in type II diabetes)

◊ dexamethasone for the glucocorticoid receptor (targeted in inflammatory diseases)

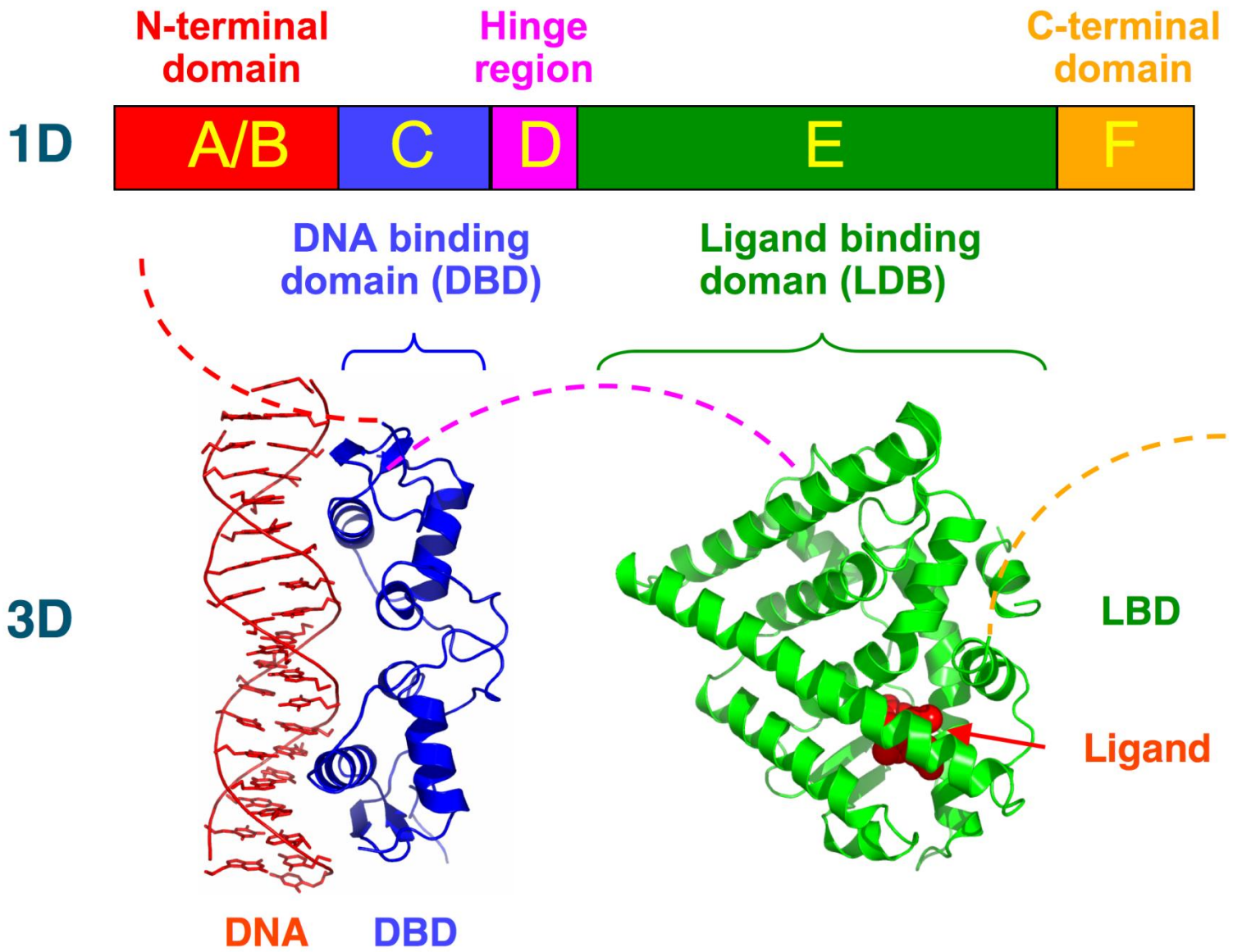
NRs classification

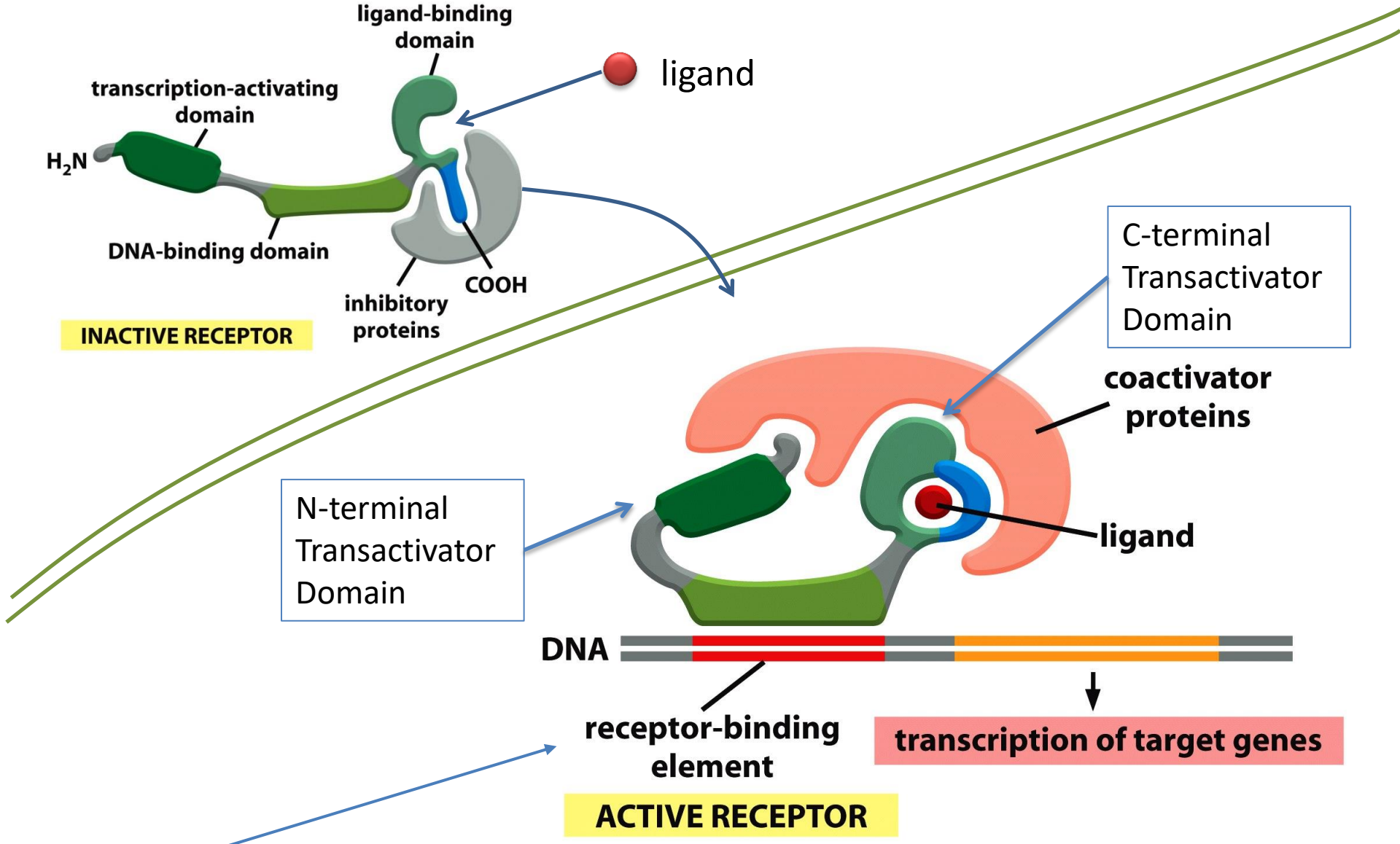
NUCLEAR RECEPTOR TYPE	NUCLEAR RECEPTOR MEMBERS
I (classical or steroid receptors)	Progestins receptor (PR) Estrogens receptor (ERα, ERβ) Androgens receptor (AR) Glucocorticoids receptor (GR) Mineralcorticoids receptor (MR)
II (RXR-heterodimeric receptors)	Thyroid hormone receptor (TRα, TRβ) All-*trans* retinoic acid receptor (RAR) 9-*cis* retinoic acid receptor (RXR) Vitamin D_3 receptor (VDR) Peroxisome proliferator receptor-γ (PPAR-γ)
III (Orphan nuclear receptors)	COUP-TFs X-linked orphan receptor (DAX-1) Rev-Erb

In H. sapiens there are 48 known nuclear receptor genes.

24 have known ligands 24 are orphan receptors

Structural Organization of Nuclear Receptors

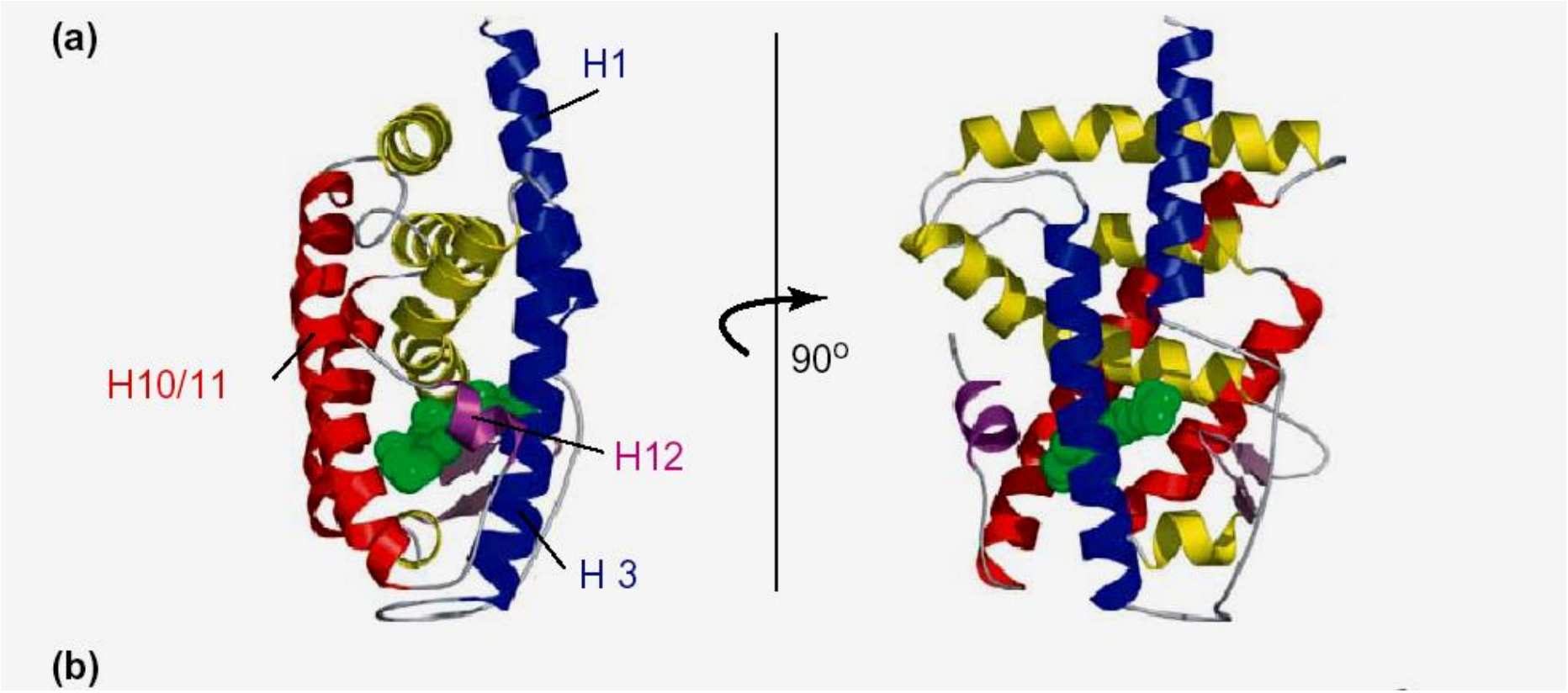




A specific 13-15 bp sequence of DNA recognized by the receptor, also called HRE (hormone response element), where receptors bind as **dimers**

Figure 15-14c *Molecular Biology of the Cell* (© Garland Science 2008)

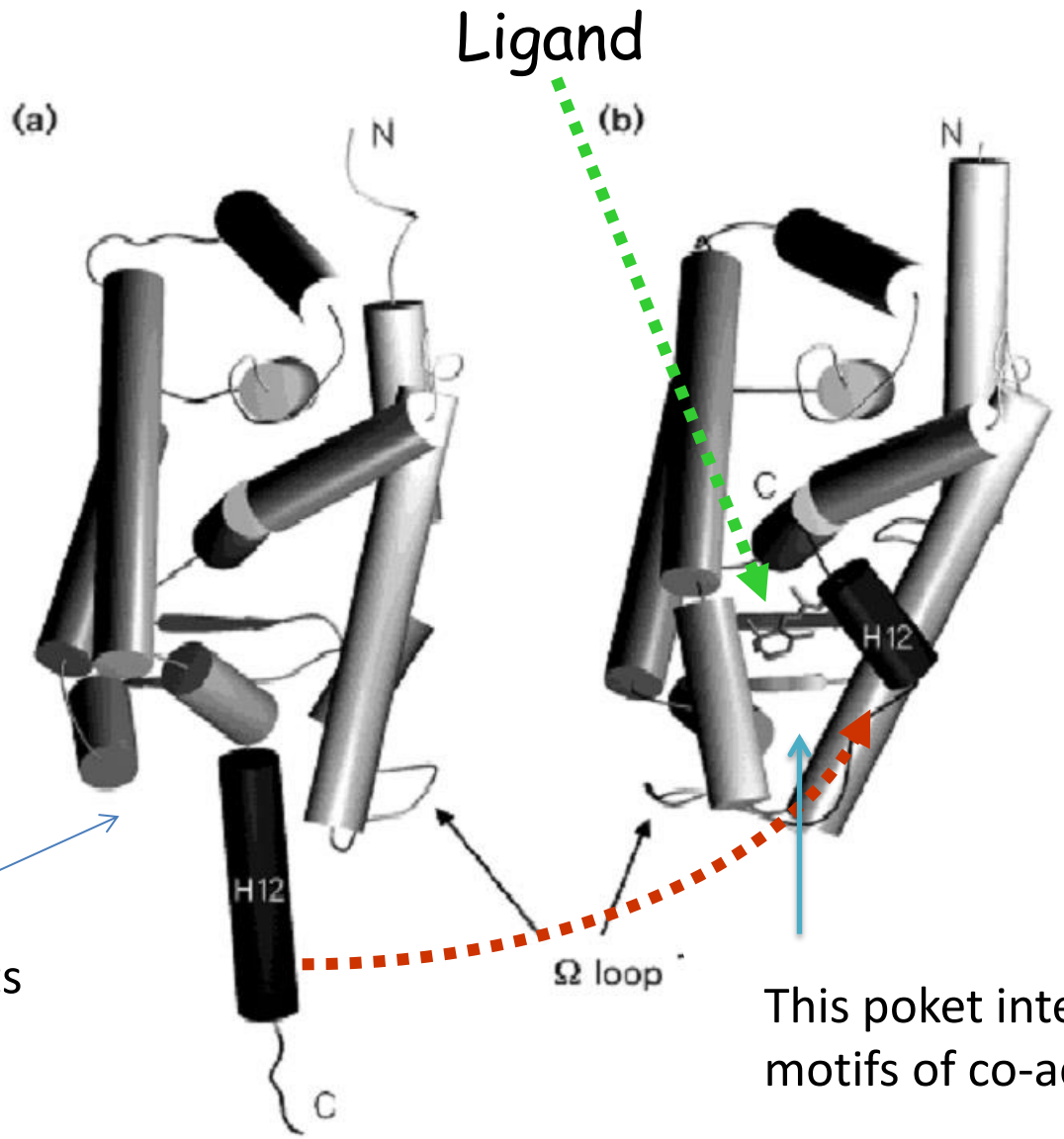
The most interaction of the Steroid Receptors with Co-Activators is mapped to the **ligand-binding domain** (LBD)



The Ligand-binding domain (LBD)

the conformational change induced by ligand binding to the C-terminal domain of NR

NR C-terminal helix (AF2) is re-positioned upon ligand binding, serving as a sort of "lid" on the ligand binding pocket

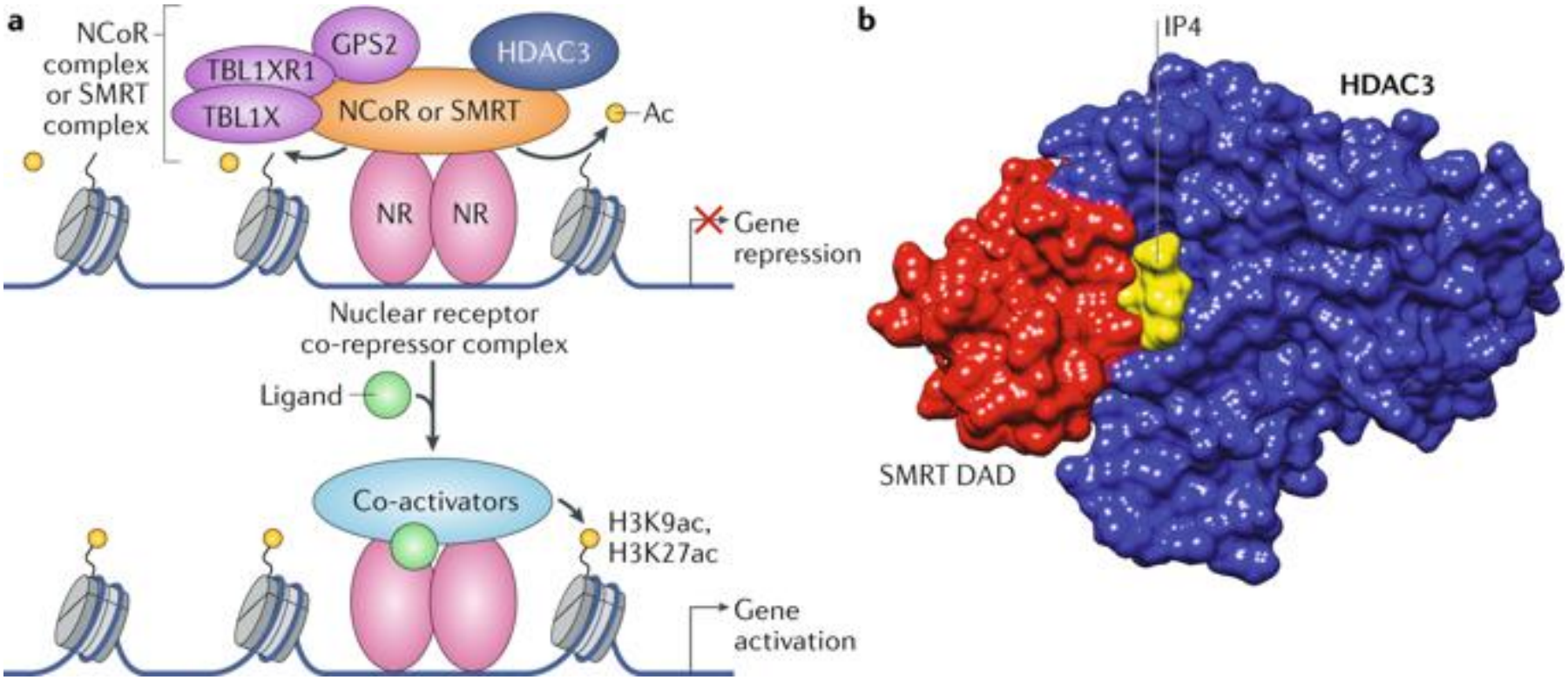


This surface interacts with **co-repressors**

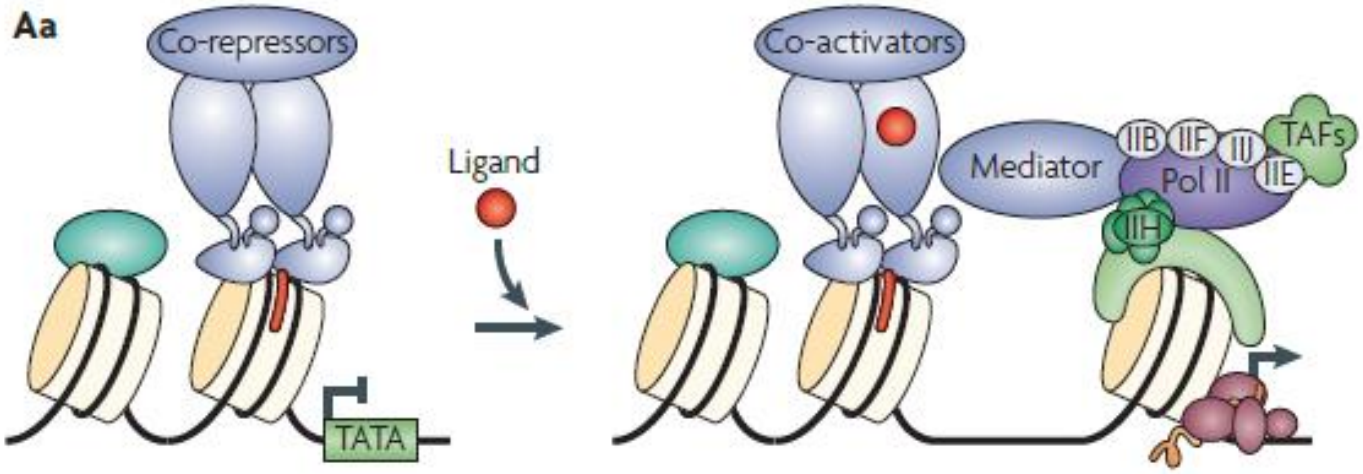
This poket interacts wi motifs of co-activators

Transcriptional Co-Repressors (CoR)

Name	Interactors	enzyme
NCoR1-NCoR2 (SMRT)	NRs, Nf-kB, MYOD, AP-1, ...	HDAC
CTBP1/2	ER, CoREST, p21, PTEN, Noxa...	HDAC
RUNX1/2/3	SMAD1/3, AP-1, ...	
CoREST	Rest, CTBP	HDAC
NURD	ER, AP-1, Twist, SNAIL, MYC ...	HDAC (*also Chromatin remodelers*)

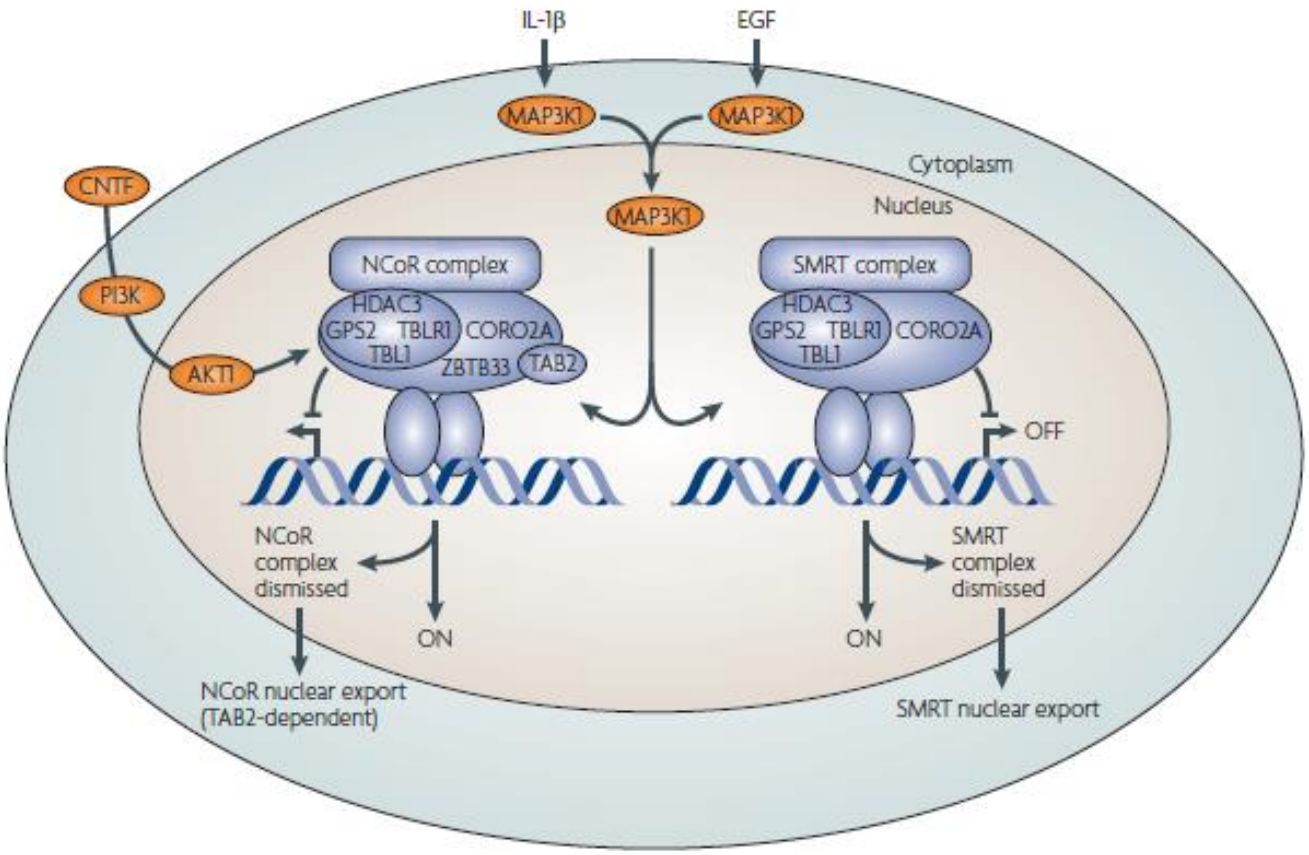

a
NCoR complex or SMRT complex
GPS2
HDAC3
TBL1XR1
TBL1X
NCoR or SMRT
Ac
NR
NR
Gene repression
Nuclear receptor co-repressor complex
Ligand
Co-activators
H3K9ac, H3K27ac
Gene activation
b
IP4
HDAC3
SMRT DAD

A number of responses are mediated by **co-repressor** / **co-activator** exchange



Perissi et al., Nat. Rev. Gentics 2010, 11:100-112.

Co-repressor dismissal depends on signalling pathways



Perissi et al., Nat. Rev. Gentics 2010, 11:100-112.