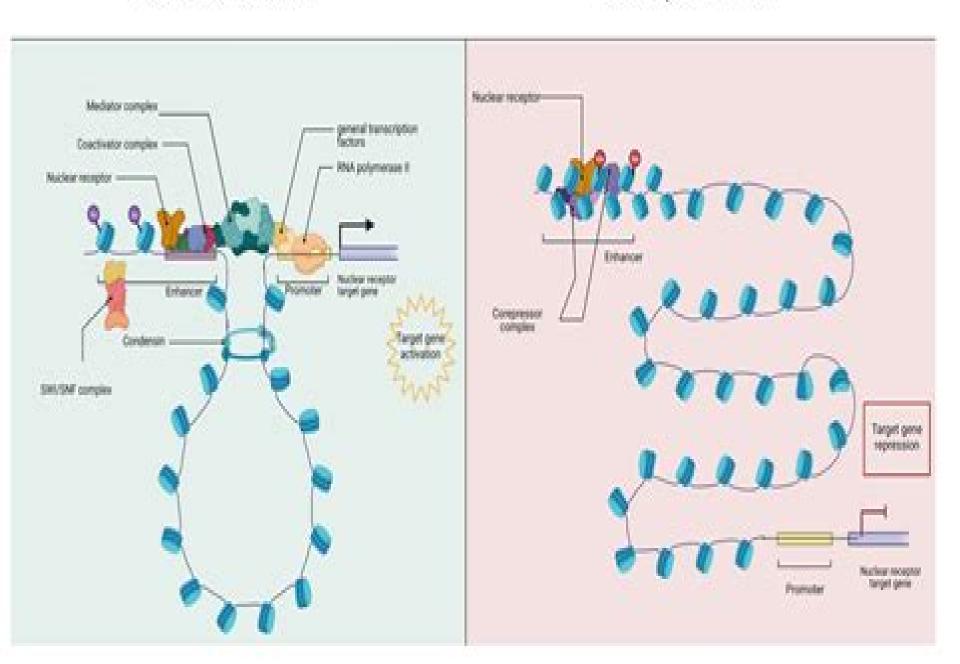
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Nuclear Receptor Coregulators

Rongrong Fan, Ines Pineda-Torra, Nicolas Venteclef

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signaling in adrenal cortex alters SF 1 containing chromatin modifying complexes during the early phase of transcriptional induction of CYP17 Chromatin IP ChIP and mammalian two hybrid experiments identified complexes which are cAMP inducible but sensitive to the SF 1 antagonist sphingosine SF 1 PTMs at the ligand binding pocket opening were found to be required for CYP17 transcription Last certain corepressors are protein kinase A PKA targets and are functionally sensitive to PKA dependent NADH accumulation Thus signaling metabolism and transcription are integrated Receptor Coregulators in Hormone Resistant Breast Cancer, 2000 To determine whether the agonist activities of tamoxifen are exaggerated in hormone resistant breast cancers Scope We proposed that coregulatory proteins influence the direction of transcription by antagonist occupied steroid receptors. We screened for such proteins and identified three novel cDNA fragments encoding peptides that interact with antagonist bound PRs The aims were to clone the complete cDNAs and define their structure Aim 1 define the role of the unknown proteins on receptor activity Aim 2 and if appropriate determine the role of these proteins in hormone dependency of breast cancers Aim 3 Major Findings Results We have focused on one novel cDNA fragment designated ORF g3 We cloned the full length cDNA assembled its genomic structure localized the gene to chromosome I 5q23 I expressed the full length protein defined its tissue distribution determined its subcellular localization to be cytoplasmic and generated a polyclonal antibody that probes a 103 kDa protein Functional studies have been completed The protein is not a ligand specific transcriptional regulator but does affect overall transcription Antisense studies show ORF 93 also blocks corepressor action on ER The protein does not affect PR nuclear translocation but interacts also with hsp90 Significance We now believe that ORF 93 has a cytoplasmic scaffolding function and allows receptors to interact with other proteins in multiprotein complexes perhaps in association with hsp90 If so ORF 93 may be important for cross talk between growth factor and nuclear receptor signaling pathways **Genetic Steroid Disorders** David M. Lonard, Bert W. O'Malley,2013-08-22 Nuclear receptors are transcription factors that bind steroid retinoid and thyroid hormones and other ligands to drive hormone dependent gene expression in conjunction with co activators and co repressors collectively referred to as co regulators So far more than 400 co regulators have been reported in the literature and they have been implicated in a wide variety of pathological conditions genetic syndromes and in cancer A key feature of co regulator based disease is the pleiotropic effects that disruption of normal co regulator function has on energy metabolism neurological function and susceptibility to cancer Technological advances in proteomics genomics and transcriptomics are leading to new ways to understand the pleiotropic actions of co regulators We expect that co regulator omics will lead to ways of understanding how co regulators can be evaluated in the context of other complex genetic factors hormones diet the environment and stress The broad role that co regulators have in human pathological conditions makes it important to consider them as important new drug targets such as for the treatment of hormone dependent cancers or for indications related to energy metabolism Better system wide knowledge of co regulator control of transcription and physiology is expected to lead to the best placement for

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